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LATE RESULTS IN TREATMENT OF AMEBIC ABSCESS AND HEPATITIS OF THE LIVER.

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Success in the treatment of amebic abscess of the liver may be held to be some measure of the efficiency of the procedure employed. Certainly invasion of the liver by the parasite—an indication of its extension beyond the wall of the bowel—is a serious manifestation of the disease. Evidence of this is afforded by the high mortality which occurred prior to the introduction of emetine by Sir Leonard Rogers.[4] Although emetine serves to control the acute manifestations of the infection, it has been difficult to eradicate the parasite completely. We have reported, from time to time, improvements in treatment which have proved most effective, but we were curious as to the late results we had obtained among patients who had hepatic involvement. In reviewing the records of the past 18 years we find that 18 patients who had an abscess of the liver have come to operation and that 17 others have been regarded clinically as presenting signs of hepatic involvement. Drainage or aspiration of an abscess of the liver with identification of the ameba in the pus is definite proof but it is not possible to prove actually that hepatic damage occurred in the patients not operated on.

One might expect that amebic abscess of the liver would be uncommon in the North Temperate Zone. Hence, it was surprising to

find that the ameba was the cause of the abscess in 18 (14%) of 125 cases of abscess of the liver encountered at The Mayo Clinic. The actual incidence of amebic abscess of the liver and hepatitis in relation to amebiasis itself is small, that is, approximately 2 or 3% of the cases, in our practice. This would seem a fairly accurate incidence for the north, barring massive infections such as occurred in the Chicago epidemic, but is, by no means, indicative of what may be the incidence in the south and in the tropics.

That the resistance of women is greater than that of men would again seem to be substantiated among patients who have hepatic damage due to the ameba. Of the 18 surgical patients, all were men and only 4 of the 17 medical cases were women; thus, 4 of the 35 patients were women. Although age is of no particular importance, the average is in the fourth decade with a range from 17 to 59 years. It has been noted in similar discussions that an associated or even antecedent diarrhea may be absent. It bears repetition to stress that 8 of these 35 patients did not have diarrhea; nor was there a history of diarrhea. Pain, usually in the right upper quadrant, was the most frequent symptom. Pain also was noted in the lower right portion of the thorax, epigastrium, and in the left upper quadrant. Reference of pain to the right shoulder was noted in 8 instances and to the left shoulder in 1 instance, indicating diaphragmatic irritation. Likewise, fever was a common symptom, although not present in 4 cases at the time of the patient's admission. Fever associated with chills had occurred in 15 cases.

The composite picture is that of a middle-aged man, with or without a history or the presence of diarrhea, who suffers with pain in the upper right quadrant. This pain is a steady soreness which varies in intensity but is not like the colic usually associated with disease of the gall bladder. Fever, 1 to 5° above normal, is associated with the pain. The pain is likely to be referred to the shoulder. Leukocytosis is present but both fever and leukocytosis may be minimal during a quiet phase. On physical examination there may be tenderness of the liver which may be elicited only by compressing the lower ribs or by a thrust of the examining hand against the liver when the patient inspires deeply. Roentgenologic examination of the chest may reveal elevation of the right half of the diaphragm and may even give evidence of fluid in the lower right portion of the thorax (10 of 29 cases). A mass in the region of the liver or enlargement of the liver is often present (8 of 35 cases). Occasionally, a draining sinus, the walls of which seem to be disintegrating, is present, if an operation has been performed previously (9 of the 18 surgical cases). Jaundice may be present but it is not intense (noted in 9 of 33 cases). Examination of the stool and pus from the abscess, if available, should be positive although repeated search may be required. In this series, criticism may be directed toward the fact that stools positive for the ameba were found in only 26

cases. In 6 additional instances, pus from the abscess was found to contain the parasite. The 3 patients, examination of whom gave no actual proof that amebas were present in stools or pus, responded so characteristically to antiamebic treatment that we make no apology for including them. "Never" is a poor word to use but, to date, we have "never" seen any disease that is so definitely improved by treatment within 36 to 48 hours as amebiasis after emetine is administered (3 to 4 grains); this improvement is apparent to both patient and physician.

As additional evidence of severity of infection, if the patient's condition permits, ulcers may be visualized through the proctoscope (7 of 17 patients examined) and the barium enema may show ulcerative changes, usually in the cecum (3 of 13 patients examined). In our series, the patients who were severely ill were not examined by these two methods.

If it is known that the liver is damaged, the extent of such damage may be determined partly by use of the bromsulphalein test. Of 7 medical cases, 5 did not give evidence of retention of the dye and 2 gave evidence of retention graded 1 to 2 (on the basis of 1 to 4). Of 6 surgical cases, 3 gave evidence of retention of dye graded 1, 2 graded 2, and 1 graded 4.

Result of Treatment in Medical Cases. Fourteen of the 17 patients are available for study of late results. Of the remaining 3, 1 died within 32 hours after admission. He was *in extremis* and so little could be accomplished that the diagnosis of perforation of amebic cecal ulcers and amebic abscess of the liver was not established until necropsy. The other 2 patients were seen in 1919 and in 1922 and we could obtain no recent data. The results of treatment of the remaining 14 patients may be noted in Table 1.

TABLE 1.—RESULTS: MEDICAL TREATMENT OF AMEBIC INFECTION OF LIVER.

Case No.	Date first seen.	Latest information.	Condition.
1	1933	Dec., 1937	Apparently well
2	1934	1935	Apparently well
3	1934	Jan., 1938	Apparently well
4	1932	Jan., 1938	Apparently well
5	1935	Jan., 1938	Apparently well
6	1934	Jan., 1938	Apparently well
7	1934	Months later	Unknown
8	1932	Dec., 1937	Apparently well
9	1933	Dec., 1937	Apparently well
10	1934	Sept., 1937	Apparently well
11	1934	Jan., 1938	Apparently well
12	1935	Jan., 1938	Apparently well
13	1935	Dec., 1937	Apparently well
14	1928	Months later	Unknown

It would be presumptive for us to use the word "cure"; but it is encouraging to have this group, each member of which gave clinical evidence of a serious condition which disappeared, as if by magic,

after antiamebic treatment. In view of their history of symptoms antedating treatment and the fact that little, if any, difficulty has been experienced since then, one cannot help but feel that a suitable régime has been employed. One example should be mentioned which might be considered as a damper against unwarranted therapeutic claims. Case 6 represents the only patient in this medical group concerning whom the question of adequate antiamebic therapy was raised and in whom the classical signs of hepatic damage later developed. He was seen at the clinic, for the first time, in 1926 because of bloody diarrhea which was found to be due to *E. histolytica*. He received emetine and 4 times he received a course of 15 tablets of stovarsol. The response was characteristically excellent and he remained well until December, 1933, at which time he developed pain in the region of the liver. On readmission, in March, 1934, examination of the stools again gave positive results for *E. histolytica*. There was marked tenderness over the left lobe of the liver and he had fever and leukocytosis. Emetine and treparsol were administered and all symptoms abated; in 48 hours he said he felt well. Further treatment with emetine and treparsol was carried out at home and on his visit here in January, 1938, he was in fine health. Examination of stools gave negative results for *E. histolytica*. We are inclined to consider this patient as an example of reinfection rather than one of exacerbation, because he has been well for 7 years.

We do have record of 3 of this medical group who had received some antiamebic therapy but it had been scanty and unsystematic; such treatment, we know, is not conducive to good therapeutic results. Although 2 or 3 years may be too short an interval of time to permit unwarranted therapeutic claims, yet the illness that preceded treatment in each case and the good health subsequent to treatment make it difficult to avoid enthusiasm.

Surgical Cases. Considering the surgical aspect of these 18 patients, one is impressed by the difficulty encountered in establishing a correct diagnosis. We realize that amebic abscess of the liver is, by no means, as frequently a surgical problem as disease of the gall bladder, ruptured ulcer, or even a lesion in the hepatic flexure of the colon, yet the presence of an abscess in that region should arouse suspicion. Usually the pus is characteristic, a dark reddish, chocolate-colored material which is rather thick. This material continued to drain from several patients without decreasing in amount, as one would expect of a pyogenic abscess. With persistence of drainage, there may be a melting away, a digestion, of walls of the sinus tract. In 1 instance, this had progressed until the patient had a hole in his epigastrium large enough to admit a fist. The digestive feature was recognized and attributed to pancreatic ferments from drainage of what was probably a pancreatic cyst. When the thick, dark, sullen flowing pus finally was examined for amebas, the

problem was settled and after treatment was instituted, filling in of the huge hole was merely a matter of a few days.

The presence of fluid in the right side of the thorax has proved misleading. Drainage through the region of resected ribs has been undertaken, the opening later being enlarged, and the etiologic factor being discovered only after the pus was examined for amebas. Also, we have had the experience of pus obtained from a draining sinus being sent "for culture" and for the usual bacteriologic studies, which delayed diagnosis for days until it was reported that "amebas have not been found." Apropos of this, Magath[3] has pointed out to us that the first pus obtained, or even that from a dressing is not likely to reveal the parasite; he makes a practice of obtaining material from the sides or edges of the sinus tract, because it is there that the parasite is working and living. We are apt to forget that the word "histolytica" means "dissolving tissue" and, therefore, it is not surprising that *E. histolytica* stays close to its base of supplies, in the walls of the sinus tract.

Eleven of the 18 patients had been operated on prior to admission to the clinic. One of them was a patient whose condition we had diagnosed as amebic colitis and who returned home to carry out treatment. He failed to complete his regimen and developed a mass in the region of the liver which his doctor drained through the side. Two patients had received much antiamebic treatment but before admission to the clinic, in spite of the treatment, an abscess had developed which was aspirated in one case and drained in the other. In both, the abscess persisted and was present on admission to the clinic. Eight of the patients stated that abscesses of unrecognized etiology had been drained and the drainage had persisted from 1 to 10 months. It was remarkable that 7 of these 8 patients had maintained even a moderately fair level of resistance. The resistance of the eighth patient was greatly depleted even though his abscess had drained for only a month. Effort was made to afford better drainage and he also received 6 grains of emetine hydrochloride, but to no avail, and he died within 48 hours.

Three patients who had been operated on elsewhere and who, when admitted, had draining sinuses, were not operated on here. Examination of material from the walls of the sinus revealed the parasite and institution of antiamebic therapy relieved the surgeon of further care of the patient. Operations were undertaken at the clinic on 15 patients. We noted, in the preceding paragraph, the patient *in extremis* who died within 48 hours. A second patient underwent drainage of a large right subphrenic abscess and only after some further time elapsed was the pus examined for amebas. Specific treatment was administered over a period of about 3 weeks but was of no avail in preventing his death.

The following operations were carried out on the remaining 13 patients: aspiration of the left side of the thorax (2 cases), estab-

lishment of drainage through resection of a low right rib (4 cases) on the lateral side, and drainage through the abdomen (7 cases). Antiamebic treatment was instituted as soon as the diagnosis was established.

The most dramatic case that we have encountered was that of a man (reported previously) who, when first seen at the clinic, was unable to lie down; he was thin and very weak. He was scarcely able to breathe because of a constant cough productive of thick, dark-colored, foul-smelling sputum. On the lower right portion of the thorax were scars of a recent rib resection. He had a moderate diarrhea which added to his sorrows. The temperature was 100.5° F. (38.1° C.) and the pulse rate was 150 beats per minute. The preliminary suggestion had been made that carcinoma of the lower lobe of the right lung was present. An alert resident physician had sent the sputum and stool for examination for amebas. *E. histolytica* was present in the stool and immediately treatment was begun. Twice, the lower right portion of the thorax was aspirated and, following these procedures, the abscess ruptured spontaneously through the old scar. Release of much purulent material, in which *E. histolytica* was identified, contributed greatly to the patient's relief. He remained here for several weeks at the end of which time he seemed to have recovered completely. A report, 2 years later, spoke of no further trouble. In this patient, the abscess of the liver had ruptured through the diaphragm and into the bronchial tree.

The question often arises, if you could establish the diagnosis, could not operation be avoided? Yes, we feel it might, as judged on the basis of experience with the 18 medical cases. On the other hand, occasionally there was a patient (2 in our series) of whom abscess of the liver was suspected. Much antiamebic therapy was administered; yet, neither of these 2 patients was able to absorb the large collection of fluid and, therefore, open drainage was necessary. In fact, 1 patient had undergone aspiration of the region of the abscess three times, only to suffer prompt refilling of the cavity. The general impression must hold that development of an abscess is unlikely if the patient has received adequate treatment. The 2 patients first mentioned must be exceptions that prove the rule.

Table 2 summarizes data concerning the 18 patients who underwent operation. The treatment of 1 patient (Case 16) must be considered a failure. Following operation and treatment at the clinic in 1919, he remained in apparently excellent health until 1925 when he had an attack of bloody diarrhea which was diagnosed as amebiasis. This was fairly well controlled until 1931 when another abscess of the liver developed. We are indebted to his physician for the data of 1925 and 1931. Again the question arises concerning whether this represented a relapse (6-year interval) or a reinfection.

As a corollary, we have record of 4 patients (all men), who gave a history of having undergone an operation for amebic abscess of the

liver. One patient (seen at the clinic in 1925) was operated on in South Africa in 1906 and must represent one of the few persons who were hardy enough to survive what was probably amebic infection in days when no specific treatment was known. A second patient had undergone drainage of an abscess on three occasions in a period of 3 years. At this time, he was having moderate diarrhea and beginning to sense pain in the region of the liver. *E. histolytica* was identified in the stool. Treatment was apparently successful and, 10 years later, he reported no further trouble. A third patient had undergone drainage of an abscess of the liver in 1927, followed by some antiamebic treatment. On examination in 1929, there was no evidence of abscess of the liver but he did have a granulomatous mass in the rectum which, it was thought, might be carcinoma.

TABLE 2.—RESULTS: SURGICAL TREATMENT OF AMEBIC ABSCESS OF LIVER.

Case No.	Date first seen.	Date last report.	Condition.
1	1928	1930	Apparently well
2	Oct., 1936	Dec., 1937	Apparently well
3	Aug., 1937	Jan., 1938	Apparently well
4	1920	1937	Apparently well
5	1925	1937	Apparently well
6	1924	1928	Apparently well
7	1930	1938	Apparently well
8	1929	1938	Apparently well
9	1931	1938	Apparently well
10	1930	1938	Apparently well
11	1927	1938	Apparently well
12	1927	1935	Apparently well
13	1928	1937	Apparently well
14	1930	1937	Apparently well
15	1928	1934	Well (died of other causes)
16	1919	1932	Recurrence? 1925
17	1925	Died post-operatively	
18	1932	Died post-operatively	

E. histolytica was identified in the stool and specific treatment brought about an apparent cure. The fourth patient gave a history of having had an abscess which had been drained on two occasions and he stated that it was amebic. He had no evident amebiasis when examined at the clinic. Hence, some few patients may not only survive operation for unrecognized amebic abscess of the liver but have little or no further trouble. These must be hardy, tough individuals and one cannot bank very heavily on such good fortune to often repeat itself. Even though it may be all but impossible to make a correct preoperative diagnosis, microscopic examination of the pus from any liver or right pleural abscess should quickly establish the diagnosis. It bears repetition to urge care in obtaining material for examination and not to be turned aside too easily by one report of negative findings. It is not scientific medicine but a

life may be saved by empirically administering emetine, if skill in the recognition of *E. histolytica* is lacking.

Another question has been raised regarding the danger of using arsenic in the presence of amebic abscess of the liver. Our experience obviously is small, as represented by these few cases; in fact, 3 of the 18 surgical cases were encountered before we used arsenic routinely. We can state, however, that we have seen no untoward results from the use of arsenic. On the contrary, we have seen failure to respond rapidly and fully until arsenic was administered. There is always the factor of individual tolerance to the drug, for which one must always be on guard, but, other than this, we have no hesitancy in advising the use of arsenic. One might coin the slogan, "Emetine to check the acute symptoms and arsenic to wipe out the amebas." Our present method of treatment is summarized as follows:[2] "If the patient is quite ill, he is kept in bed for the first few days; if he is not particularly ill, hospitalization is not necessary. Obviously the diet may need to be bland and simple if there is much dysentery, but very rapidly, that is, within 24 to 48 hours, a full and generous diet is begun. . . .

"If the patient has not received antiamebic treatment recently, he is given 0.065 Gm. (1 grain) of Burroughs, Wellcome & Co. emetine hydrochloride, subcutaneously, twice daily for 3 days. After an interval of a week, 0.043 Gm. (two-thirds grain) of emetine is given twice daily for three more days. With the institution of the emetine, treparsol, 0.25 Gm. (4 grains), is administered orally with each meal for four days. If there is no intolerance to arsenic, two more such courses are prescribed with intervals of ten days between the courses. . . .

"If stool tests are positive following this regimen, three courses of chiniofon are prescribed: 3 Gm. orally per day for a week and repeated for two more such courses, with a week's interval between courses. If diarrhea is increased, the daily dose is decreased, thereby prolonging each course. Failure after this would indicate a course of one injection of arsphenamine weekly for six weeks, and 1 drachm (3.88 Gm.) of bismuth subnitrate from three to six times daily during the period."

Summary. Invasion of the liver by *E. histolytica* is a serious complication of amebic infection. The diagnosis of involvement of the liver is suggested by the symptoms of pain in the upper part of the abdomen, often referred to the shoulder, by fever, chills, leukocytosis, and, usually, but not always, an associated diarrhea or history of diarrhea. Unless an abscess develops which is aspirated or drained, it is not possible to prove that the liver is involved. However, such a syndrome as listed above, which is relieved by antiamebic treatment is all but proof of amebic infection. As a corollary, a similar picture uninfluenced by antiamebic treatment is not amebiasis, except in the rare instances of a huge collection of

pus which must be drained and then, of course, the proof of *E. histolytica* should be promptly obtained. Faith in the efficacy of our medical treatment would seem supported by the results in these cases; not that we have ceased trying new drugs, but until just as effective ones with even less toxicity than we now encounter are available, we feel justified in considering emetine and treparsol as the backbone of our treatment.

Regarding our surgical cases, it is obvious both from clinical experience as well as from this review, that the correct preoperative diagnosis of amebic abscess of the liver is by no means easy. However, if the surgeon encounters an abscess in the upper right portion of the abdomen, the source of which is not obvious or, if there is fluid in the thorax (as a result of extension from the liver through the diaphragm) and the material from the abscess is thick and dark in color, it is difficult to think of allowing such an abscess to remain undiagnosed without performing an examination for *E. histolytica*. Figures will vary with material available for study but probably 10 to 15% of abscesses of the liver seen in the North Temperate Zone are due to *E. histolytica*.

REFERENCES.

(1.) **Brown, P. W.**: Am. J. Med. Sci., **179**, 264, 1930. (2.) **Brown, P. W.**: J. Am. Med. Assn., **105**, 1319, 1935. (3.) **Magath, T. B.**: Personal communication. (4.) **Rogers, L.**: Recent Advances in Tropical Medicine, Philadelphia, P. Blakiston's Son & Co., 1928.

THE "HÆMATOPOIETIC PRINCIPLE" IN THE DISEASED HUMAN LIVER.*†

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In 1932, Richter, Ivy and Kim[3] reported the presence of the "specific anti-anemic substance" in an extract obtained postmortem from the liver of a treated case of pernicious anemia and its absence from the liver of an untreated patient with this disease. They assumed, therefore, that when the specific anti-anemic substance is administered to a patient with pernicious anemia the liver stores it. Their observations were confirmed by Wilkinson and Klein[4] and by Goldhamer, Isaacs and Sturgis.[1]

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† This study was made possible by a special grant from Parke, Davis & Co.

Wintrobe and Shumacker[6] (1933), and Wintrobe[5] (1936) called attention to the association of macrocytic anemia and liver disease and on the basis of clinical and pathologic studies advanced the hypothesis that this anemia may be due to inability of the diseased liver to store the anti-anemic substance. As far as we were aware, the only direct proof of this assumption was the observation of Goldhamer, Isaacs and Sturgis that an extract prepared postmortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hematopoietic response when administered parenterally to a patient with pernicious anemia in relapse. This observation, together with other experimental data, led them to conclude that the specific hematopoietic substance might not be stored by a severely damaged liver, or even though stored, might not be delivered to the tissues. It therefore appeared to us desirable to obtain additional data on the presence (or absence) of the anti-anemic substance in the diseased human liver.

Method. Extracts were made from a normal calf's liver and from 5 diseased human livers according to the following method, kindly furnished us by Dr. Raphael Isaacs,[2] which is essentially that of preparing Cohn's fraction G: "Suspend 500 grams of liver finely chopped in 1 liter of water and stir thoroughly. Heat this on a steam bath to 80° C. until the protein appears to be precipitated. Filter. Add enough concentrated hydrochloric acid to the filtrate to precipitate the acid-coagulable protein. Filter. Concentrate under reduced pressure to 300 cc. and add enough 95% alcohol to make the solution 70% alcohol. Filter. Remove the alcohol under reduced pressure. Concentrate the remaining fluid to 100 cc. Filter."

The patients selected for injection had typical pernicious anemia with a red cell count between 1 and 3 million per c.mm., had received no anti-anemic treatment in the form of liver, iron, arsenic or transfusions for at least 1 month prior to the injection, were free of infection (with one exception) and subsequently showed a complete remission under specific treatment.

Before preparing the extracts of the human livers, a control extract was made from a normal calf's liver and administered intramuscularly to a patient with pernicious anemia. A satisfactory response was obtained (Fig. 1).

Extracts were then prepared from the livers of the following patients with hepatic disease:

Case 1. *Extract from G. H. (No. 360238), patient with hepatic cirrhosis.* The patient was a male, aged 54 in whom a diagnosis of hepatic cirrhosis was made 2 years prior to death. The diagnosis was based on the presence of an enlarged firm liver and an enlarged spleen together with a strong alcoholic history. The blood Wassermann test was negative. There was no anemia and no history of hematemesis. On March 1, 1936, he was hospitalized because of ascites. At that time, the red count was 3 million, the hemoglobin 68% (Sahli) and the M.C.V. 105. A post-histamine achlorhydria was present. There were no abnormal neurologic findings. There was 20% retention of bromsulphalein ½ hour after injection of 2 mg. of the dye per kg. of body weight. The Takata-Ara test was positive. The

icteric index was 11. On March 31, and again on April 1, 1936, he was given 2 cc. of a commercial liver extract intramuscularly (of which 1 cc. was derived from 100 gm. of liver) but no hematopoietic response was obtained. He was given 3 additional injections of 1 cc. of this liver extract during April, 3 in May, 2 in June and 4 in July (the last on July 31st), in spite of which there was a progressive increase in the anemia. A Talma-Morrison operation was performed on May 19th, at which time a "marked atrophic cirrhosis" was described. On August 30th, the day before death, the red cell count was 2.2 million, hemoglobin 47% and the M.C.V. 100. The patient died in coma on August 31, 1936.

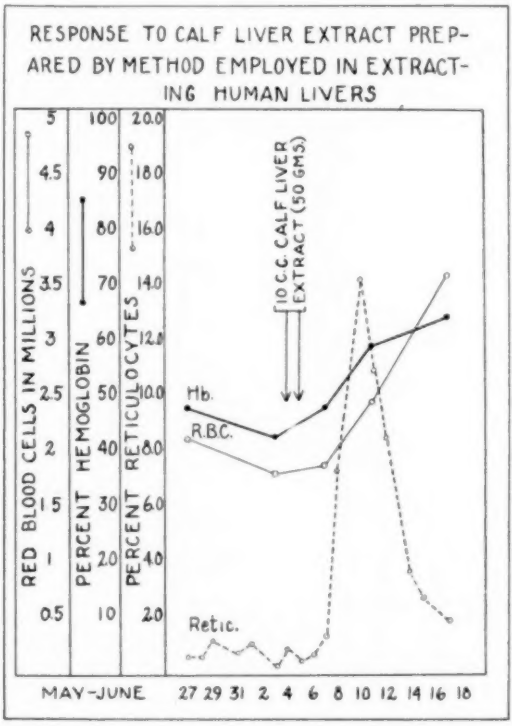
RESPONSE TO CALF LIVER EXTRACT PREPARED BY METHOD EMPLOYED IN EXTRACTING HUMAN LIVERS
RED BLOOD CELLS IN MILLIONS
PERCENT HEMOGLOBIN
PERCENT RETICULOCYTES
10 C.C. CALF LIVER EXTRACT (50 GMS.)
Hb.
R.B.C.
Retic.
MAY-JUNE
27 29 31 2 4 6 8 10 12 14 16 18

FIG. 1.

Necropsy (4 hours after death): The liver was described as small, pale yellow and finely nodular, and weighed 900 gm. Microscopic examination revealed extensive fibrosis with lymphocytic infiltration.

An extract prepared from the liver and administered intramuscularly to a patient with pernicious anemia produced a typical response (Fig. 2).

It may be argued that the hematologic response could be ascribed to the administration of the commercial liver extract, even though none had been given for a month prior to the patient's death. Regardless of this, the response obtained would indicate the ability of a diseased liver to store the anti-anemic substance.

CASE 2. *Extract from L. K. (No. 16423), patient with hepatic cirrhosis.* The patient was a painter, aged 32, who was first admitted to the medical service on December 24, 1933, because of hematemesis. He had had intermittent digestive distress including pain in the epigastrium occurring immediately after meals for 4 years. There was a strong history of alcoholism. He was found to have an enlarged liver and spleen with no evidence of ascites. There was 30% retention of bromsulphalein ½ hour after the injection of 2 mg. of the dye per kg. of body weight. The icteric index was 11. The blood Wassermann test was negative. A gastro-intestinal Roentgen ray series showed no evidence of peptic ulcer. The blood count on discharge was 3.2 millions with 45% hemoglobin. The gastric contents contained free hydrochloric acid.

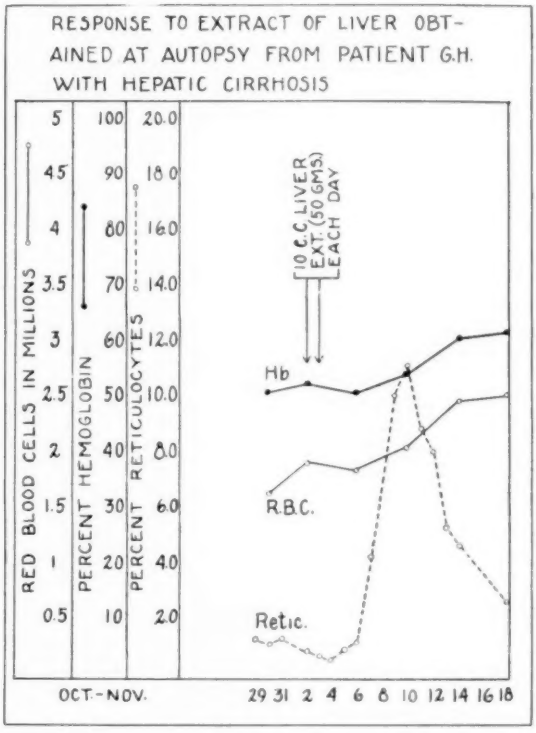

FIG. 2.

He was again seen on June 11, 1935, at which time he presented much the same findings except that his liver was not palpable, there were very prominent superficial veins, and ascites and slight icterus were present. The icteric index was 19. The Takata-Ara test was positive. The blood count showed 60% hemoglobin with 2.9 million red cells. Macrocytosis was prominent in the stained blood smear. The M.C.V. was 100. The patient died 6 days after admission following massive hematemesis. He had at no time during his illness received any anti-anemic therapy other than iron.

At *necropsy* a ruptured esophageal varix was demonstrated. The liver, which weighed 1600 gm., was described as tawny yellow, coarsely nodular and of extremely firm consistence. Microscopic sections revealed extensive fibrosis, lymphocytic infiltration and apparent bile duct proliferation.

An extract prepared from this liver yielded a satisfactory response when administered intramuscularly to a patient with pernicious anemia (Fig. 3).

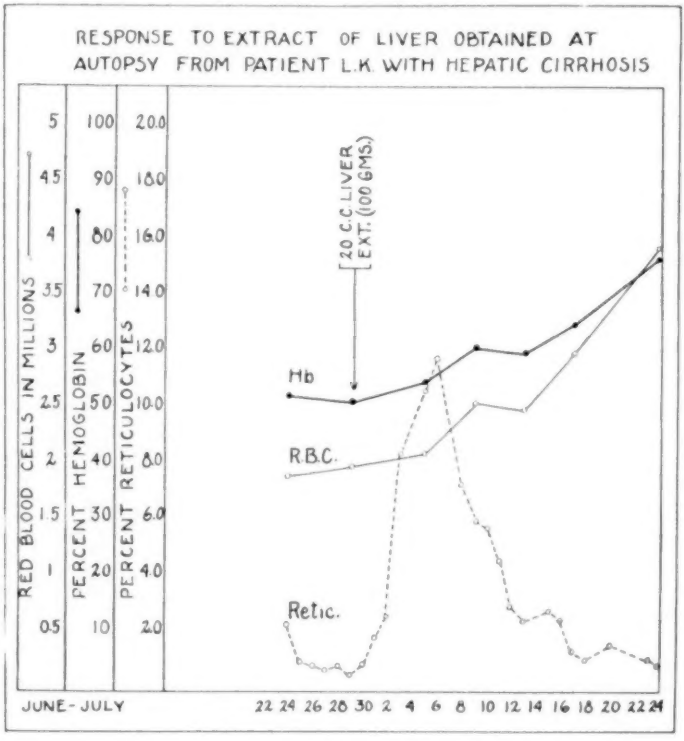
RESPONSE TO EXTRACT OF LIVER OBTAINED AT AUTOPSY FROM PATIENT L.K. WITH HEPATIC CIRRHOSIS
RED BLOOD CELLS IN MILLIONS
PERCENT HEMOGLOBIN
PERCENT RETICULOCYTES
20 C.C. LIVER EXT. (100 GMS.)
Hb
R.B.C.
Retic.
JUNE - JULY
22 24 26 28 30 2 4 6 8 10 12 14 16 18 20 22 24

FIG. 3.

CASE 3. *Extract from F. R. (No. 28478), carcinoma of the hepatic duct with cirrhosis and hepatic metastases.* The patient, F. R., a female nurse aged 45, was admitted to the medical service of this hospital on September 7, 1934, complaining of jaundice of 1 week's duration which had been preceded for several days with fever, chills, nausea, diarrhea and abdominal pain. There was no history of alcoholism. There was a history of nervous indigestion following a back injury 3 years before. Her liver was found to extend about 2 cm. below the right costal margin, while the spleen was not felt. The icteric index was 100 and the serum bilirubin 16.5 mg. %. The blood Wassermann test was negative. The hemoglobin was 90% and the red count 4.4 millions. It was at first felt that the patient had catarrhal jaundice, but because of progressive increase in the icterus (icteric index 165, serum bilirubin 25 mg. %) laparotomy was performed 1 month later. An inoperable tumor occluding the hepatic duct was found. Following operation, the jaundice remained completely obstructive as verified

by repeated stool and urine examinations. In April, 1935, the spleen became palpable and in May, ascites developed. The bromsulphalein retention varied between 80 and 100% throughout her stay. Anemia gradually developed, the red count varying between 2.8 and 3.5 millions, the hemoglobin between 61 and 70%, and the M.C.V. between 102 and 111. Free hydrochloric acid was present in the gastric contents.

The patient died in coma on July 4, 1935. The liver was described as "smaller than average," yellowish red and of increased consistence. Microscopic sections revealed diffuse fibrosis and scattered metastases.

An extract administered intramuscularly to a patient with pernicious anemia produced the effect as noted in Fig. 4.

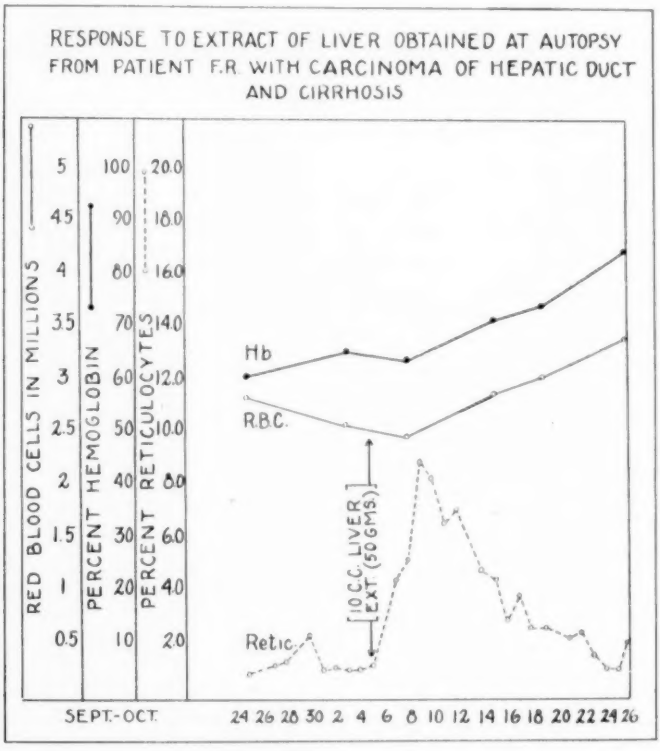
RESPONSE TO EXTRACT OF LIVER OBTAINED AT AUTOPSY FROM PATIENT F.R. WITH CARCINOMA OF HEPATIC DUCT AND CIRRHOSIS
RED BLOOD CELLS IN MILLIONS
PERCENT HEMOGLOBIN
PERCENT RETICULOCYTES
Hb
R.B.C.
Retic.
10 C.C. LIVER EXT. (50 GMS.)
SEPT.-OCT.
24 26 28 30 2 4 6 8 10 12 14 16 18 20 22 24 26

FIG. 4.

CASE 4. *Extract from J. B. (No. 24540), patient with chronic passive congestion of the liver.* The patient, a white male, aged 74, was admitted to the medical service of this hospital on December 8, 1935, with acute congestive heart failure. He had had symptoms of cardiac weakness for about 3 years and had been admitted 1½ years before with congestive heart failure, which was felt to be due to arteriosclerotic hypertensive heart disease with auricular fibrillation. At that time, he remained in the hospital for 2 weeks; signs of congestive failure including an enlarged tender liver were present. During the present admission which was of only 2 hours'

duration, there was no visible icterus, hemoglobin was 70% (Sahli) and the red cells numbered 3.9 millions. An M.C.V. determination was not done.

Necropsy (performed 12 hours after death) showed the presence of a typical nutmeg liver weighing 1805 gm., which on microscopic section showed central necrosis with hemorrhage. There was extensive generalized arteriosclerosis. An extract prepared from this liver was administered to a patient with pernicious anemia and cystitis with an effect as shown in Fig. 5. The presence of cystitis might have prevented the development of a more marked reticulocytosis, although the patient eventually had a complete remission.

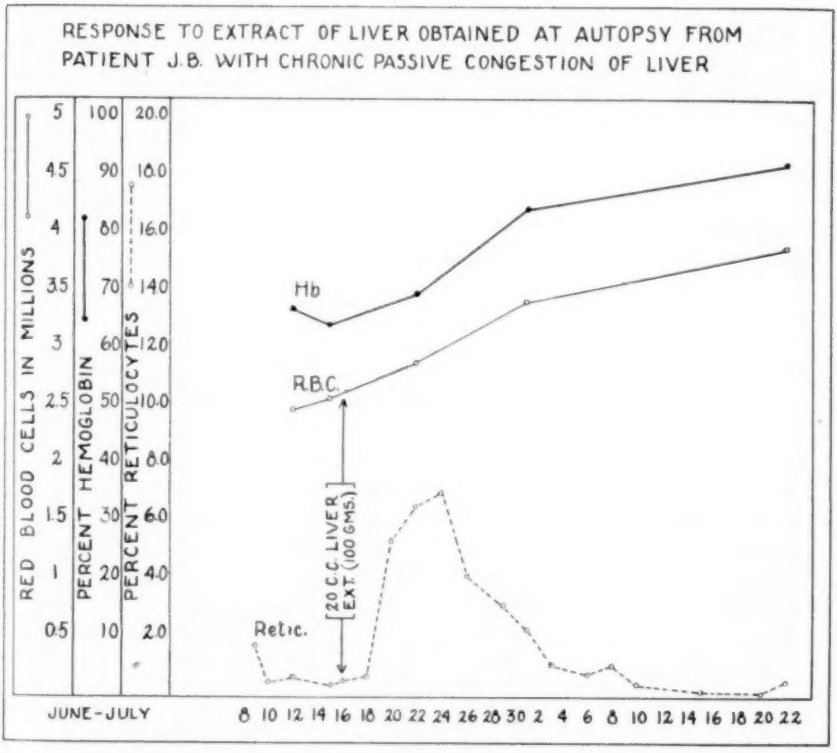
RESPONSE TO EXTRACT OF LIVER OBTAINED AT AUTOPSY FROM PATIENT J.B. WITH CHRONIC PASSIVE CONGESTION OF LIVER
RED BLOOD CELLS IN MILLIONS
PERCENT HEMOGLOBIN
PERCENT RETICULOCYTES
Hb
R.B.C.
Retic.
20 C.C. LIVER EXT. (100 GMS.)
JUNE-JULY
8 10 12 14 16 18 20 22 24 26 28 30 2 4 6 8 10 12 14 16 18 20 22

FIG. 5.

CASE 5. *Extract from H. P. (No. 46891), patient with chronic myeloid leukemia.* The patient, a white male, aged 70, was admitted to the medical service of this hospital on October 22, 1935. He complained of increasing weakness and dizziness for 2 to 3 years with marked pallor for over 1 year. Dyspnea and ankle edema had been present for 6 months. In addition to marked pallor slight fever was present. The abdomen was distended due to ascites. The liver was felt one fingerbreadth below the right costal margin and the spleen extended halfway to the left iliac crest. The white cells numbered 500,000 per c.mm. and the blood smear was typical of myeloid leukemia. The hemoglobin was 45% (Sahli) and the red cells

numbered 2.7 millions. An M.C.V. was not done. The patient died of bronchopneumonia 14 days after admission.

Necropsy was performed 3 hours after death. The liver which weighed 3480 gm. was described as large, moderately firm, and pinkish yellow. Microscopic sections revealed extensive leukemic infiltration. An extract prepared from it was administered to a patient with the result as noted in Fig. 6.

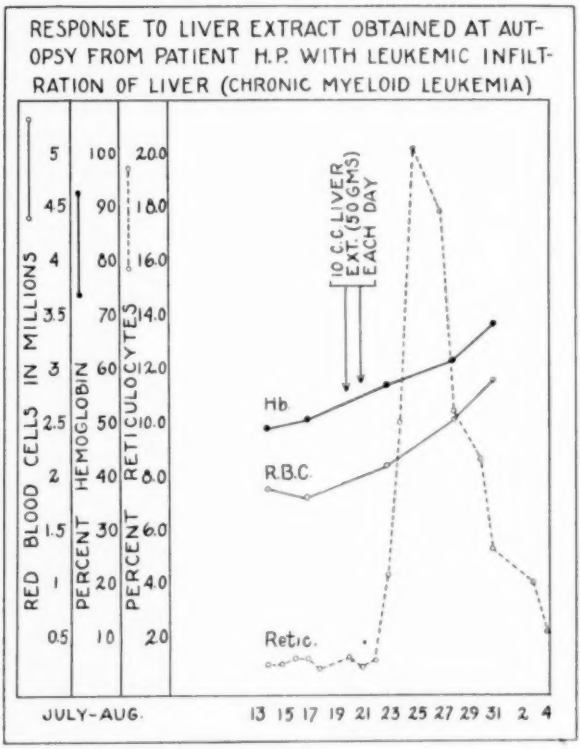

FIG. 6.

Summary. Extracts were prepared from the livers obtained postmortem from 5 patients with chronic liver disease. These included 2 examples of portal cirrhosis, 1 of obstructive cirrhosis secondary to neoplasm of the hepatic duct, 1 of chronic passive congestion and 1 of extensive leukemic infiltration. The extracts were administered intramuscularly to a suitably controlled group of patients with pernicious anemia in relapse. A characteristic reticulocytosis resulted, followed by an increase in hemoglobin and red cell count and by marked clinical improvement.

The 3 patients with cirrhosis presented a macrocytic anemia, while the type of anemia in the remaining 2 patients was not definitely determined.

Conclusion. The human liver may contain the specific hematopoietic principle even when it is the seat of extensive and protracted disease. This holds true even in the presence of macrocytic anemia. This strongly suggests that the macrocytic anemia associated with liver disease is not caused by failure of the liver to store the specific anti-anemic substance.

We wish to express our appreciation to Dr. Ralph H. Fuller, of the Department of Pathology for his coöperation in this study.

REFERENCES.

(1.) **Goldhamer, S. M., Isaacs, R.,** and **Sturgis, C. C.**: Am. J. Med. Sci., **188**, 193, 1934. (2.) **Isaacs, R.**: Personal communication. (3.) **Richter, O., Ivy, A. C.,** and **Kim, M. S.**: Proc. Soc. Exp. Biol. and Med., **29**, 1093, 1932. (4.) **Wilkinson, J. F.,** and **Klein, L.**: Quart. J. Med., **3**, 341, 1934. (5.) **Wintrobe, M. M.**: Arch. Int. Med., **57**, 289, 1936. (6.) **Wintrobe, M. M.,** and **Shumacker, H. S.**: Bull. Johns Hopkins Hosp., **52**, 387, 1933.

A CONSIDERATION OF THE PHENOMENON OF PURPURA FOLLOWING SCARLET FEVER.

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Severe purpura during the course of scarlet fever or following in its wake, has been a rare phenomenon in our experience. During the past 13 years only 2 cases of severe purpura were observed in very nearly 12,000 scarlet fever patients. Two other incidents of mild purpura have been studied. These occurred in individuals who had recently passed through a bout of scarlet fever, the purpura appearing after the termination of quarantine.

The literature contains about 50 reported cases of severe purpura occurring during the course of, or as a sequel to, scarlet fever. The rarity of the condition, therefore, warrants presentation of other cases and a discussion of the significance of this clinical entity.

We have had only two opportunities to perform necropsies on cases of scarlet fever with purpura. These 2 cases are not detailed in this series, as we do not have sufficiently accurate clinical data. In both of these the skin and viscera exhibited purpuric manifestations of a fine discrete type. The distribution of the purpura was most marked on the serous membranes, but also occurred in the bladder and intestinal tract. The significant feature of these 2 cases is that carefully performed postpostmortem cultures did not disclose streptococci in the blood or in these purpuric lesions. They were reported to us as of about 2 weeks' duration and of a fulminating type. The immediate cause of death in these cases was attributed

to severe toxemia, as there were no other significant anatomic features to which death could be attributed.

The essential gross lesions found in these cases were: A diffuse congestion of the lungs; a rather extensive pleural ecchymosis and purpura; cloudy softening of the myocardium with few fine discrete purpuric spots on the epicardium and at the base of the mitral valve; hyperplasia and swelling of the mesenteric and mediastinal lymph nodes; moderate hemorrhagic engorgement and hyperplasia of the spleen; a moist and pale liver; fine petechiæ in the gastric and intestinal mucosa, chiefly in the upper portions of the intestinal tract; moderate swelling and congestion of the kidneys without purpura; purpura in the bladder mucosa; and discrete, scattered, purpuric spots on the skin of the lower extremities. The diagnosis of scarlet fever was based upon antemortem findings and cultures from the throat. Microscopy disclosed considerable, generalized, parenchymatous swelling. The purpuric areas were not associated with thrombosis, but consisted of minute extravasations of blood, frequently perineural in distribution and often confluent to form large hemorrhages. The kidneys were not remarkable.

The following data are concerned with our clinical observations:

Clinical Abstracts. CASE 1.—A white girl, aged 13, entered the Milwaukee City Hospital for Contagious Diseases on February 11, 1937, with a history of sore throat and vomiting of 3 days' duration. On the fifth day of the disease a generalized rash appeared. The physical examination disclosed a typical strawberry tongue, injected pharynx, and a scarlet fever erythema of the skin. The temperature was 100.6°, the pulse 94 and the respirations 23 per minute. The blanching test was positive. Urinalysis did not disclose any abnormal constituents. A diagnosis of scarlet fever appeared warranted. The past medical history was entirely negative except for chicken-pox and measles. In particular, there was absence of a personal or familial history of evidences of hemorrhagic diatheses.

On the sixth day in hospital the temperature, which had been moderately elevated, returned to normal. On that day vaccination was performed. Two days prior to this there had been a moderate cervical adenitis which was now disappearing. On the tenth day in hospital stomach cramps developed, and there was a mild febrile reaction. There now appeared numerous discrete purpuric spots on the ventral surfaces of the lower extremities. The following day there was blood-tinged vomiting and more abdominal cramps. Tenderness and pain in the epigastrium developed. Large purpuric hemorrhages around the elbows and fresh crops of petechial spots over the lower extremities made their appearance on the 12th to the 14th day of the illness. Leukocyte count: 23,800 per c.mm. No hematuria. The hemorrhage in the skin continued to spread, involving the trunk and extremities, and also appeared in the conjunctivæ, scleræ, and palate. A diagnosis of Henoch-Schönlein purpura was made. Glucose and saline were administered by vein along with 80 cc. of convalescent serum. Three days after the appearance of the purpura the phenomenon was widely distributed. A whole blood transfusion was given. A blood platelet count at this time, namely, the 14th day in hospital and the 4th day of the purpura, was 300,000 per c.mm. Coagulation time and bleeding time were normal. The clot retraction was adequate. Nausea and vomiting continued along with fresh purpuric manifestations. On the 5th day of the purpura 0.2 cc.

of a 1/3000 dilution of moccasin snake venom was given subcutaneously. The following day this was increased to 0.4 cc. At this time the purpura of the face, palate, and uvula was so intense as to warrant the use of the term "infarction." Blood transfusion was repeated.

On the 8th day of the purpura the urine was quite bloody. Snake venom was increased to 0.8 cc. New purpuric areas did not appear after the 8th day of the condition. Hematuria disappeared within a day or two, although albuminuria persisted for several days. She was transferred to another institution 31 days after admission to the fever hospital. The clinical course after this was that of progressive improvement with gradual disappearance of the purpura, and at the present writing this patient has entirely recovered and does not present any abnormalities in the blood nor any evidences of purpura, even after the application of the tourniquet test. Figures 1, 2, 3, 4, and 5 are indicative of the distribution and extent of the purpura.

CASE 2.—A white female, aged 18, was admitted to the hospital January 1, 1935, having had a sore throat and vomiting for 4 days. The tongue was typically strawberry. There was an injected pharynx and enlarged cervical lymph nodes. On the day after admission to the hospital uterine bleeding began and continued for 20 days, during which time the erythrocytes in the blood were reduced to 2,640,000 per c.mm. During the period of uterine bleeding widely distributed purpuric spots, over the lower extremities, in particular, developed. On the 22d day in hospital the patient was transferred to another hospital and was given a blood transfusion. She was discharged from that hospital on February 10, 1935, free of purpura and apparently entirely well. During this period she was given moccasin snake venom once. The blood of this patient showed anemia. The platelets ranged from 190,000 to 250,000 per c.mm., the leukocytes from 5000 to 6100 per c.mm., the bleeding time, coagulation time, and clot retraction were all entirely normal.

CASE 3.—A white female, aged 22, had a mild attack of scarlet fever in 1933. After discharge from the hospital irregular uterine bleeding developed, and shortly after, within a few weeks, recurrent crops of petechiæ in the skin, particularly on the lower extremities appeared. Hemorrhages occurred in the skin upon the slightest traumatic provocation. This condition continued for about a year, during which time there were occasional attacks of hematuria, associated with renal colic. Blood transfusions were performed on 3 occasions. In the latter part of 1935 there was a moderate degree of anemia. The hemoglobin was 13.5 gm. The blood platelets were entirely within normal limits. Bleeding time, coagulation time, and clot retraction were normal. There was a slightly purpuric manifestation, chiefly on the lower extremities. The urine contained a few blood cells. The tourniquet tests were weakly positive. Recurrent abdominal pain, mostly in the right lower quadrant, was a rather prominent feature. Snake venom therapy was started, but each injection was followed by severe local reaction and purpura, and after 6 attempts this therapy was discontinued. The patient was again observed in the latter part of 1936, at which time all signs of purpura had been absent for several months, and the condition seemed to be entirely relieved. Menstruation was normal, and there was complete relief from all previous complaints.

CASE 4.—An 11-year-old boy developed scarlet fever in June, 1937. One week after discharge from quarantine purpura developed which involved the skin and mucous membranes of the mouth. At this time mild hematuria was detected. Fresh crops of purpura appeared daily for 4 days. A blood examination disclosed a mild anemia. After the 4th day of purpura, following a blood transfusion, the condition subsided, and in September, 1937, the boy appeared entirely well without any evidence of purpura and without any evidences of nephritis.

Comment. The purpuric manifestations in these cases were apparent chiefly in the skin, although the mucous membranes in 2

FIG. 1

FIG. 2

of the cases were also involved. In the first case, the hemorrhages became confluent, and local infractions resulted. Distribution over

FIG. 3

FIG. 4

FIGS. 1, 2, 3, 4 and 5.—Purpuric lesions. Case 1.

the bony prominences was a feature of this case. Prominent in all cases was the absence of detectable enlargement of the spleen or liver. In none of these cases was there any evidence of previous hemorrhagic tendencies or of familial hemorrhagic characteristics. Associated with the purpura was hematuria in all of these incidents. The hematuria disappeared with the purpura and appeared to be a part of the hemorrhagic episode. None of these cases was followed by evidences of nephritis. It would appear, then, that hematuria in scarlet fever may be a purpuric phenomenon and that in the absence of evidences of kidney damage, hematuria by itself is not evidence of scarlet fever nephritis.

Scarlet fever toxin appears to have a strong effect upon capillary endothelium. Thus, the toxin injected into the skin produces erythema, in which evidences of capillary fragility and damaged endothelium appear. This phenomenon occurs in the vascular endothelium of the glomerular tufts. The hematologic findings in our cases would seem to be of little significance so far as positive data are concerned. Except for the anemia, which responded rapidly, there was not any evidence of toxic depression of the bone marrow. Thrombocytopenia reported by others, was not a feature of our cases. Leukocytosis was not striking in our cases, although it has been reported by others.

Treatment by blood transfusion and snake venom seems to be indicated. The use of snake venom in acute nephritis has been suggested by Peck and Baehr. Snake venom was found by Peck[8] to inhibit the Shwartzman reaction, and because of the hemorrhagic features of this reaction, the use of snake venom was suggested as a means of increasing capillary resistance to the streptococcic toxin. In our experience, the value of snake venom in this condition is not established, but its use should be encouraged. Blood transfusions likewise seem beneficial. Splenectomy and Roentgen ray therapy, reported by others, seems to us unsound.

Stevenson,[15] in 1912, was able to find only 33 cases of purpura in scarlet fever. McConnell and Weaver,[7] in 1922, found about 50 cases of purpura hemorrhagica and of purpura fulminans associated with scarlet fever. In 1933, Box[2] was able to find about 50 cases recorded.

The clinical features of purpura in scarlet fever will depend upon the severity of the process. In the fulminating type the hemorrhages develop and spread rapidly. Confluence is a prominent feature. Skin and viscera are severely involved. Distribution over bony prominences is striking. The lesions may exhibit dark to black discoloration, infarction and necrosis may follow. Hemorrhages from the nose, pharynx, bowel, bladder, and kidney are to be expected. Hemorrhages into joint cavities did not occur in our cases. The spleen and liver were not enlarged. Fever is variable and may be severe. In the milder cases the hemorrhages are finer, more dis-

crete, and less apt to be confluent. Skin and visceral surfaces are involved, and the condition may become subacute or chronic and intermittent.

Hematuria is a feature of both types. The urinary sediment does not contain evidences of renal parenchymal irritation. The entire course of the hematuria and its disappearance with the subsidence of the purpura indicated rather strongly that the capillary endothelium in the kidneys has been rendered permeable as a result of the direct action of the scarlet fever toxin. As previously mentioned, scarlet fever toxin produces changes in capillary endothelium (Smith[14]). In the areas of erythema, produced by injecting the toxin, Birkhaug has demonstrated swelling of these cells. In early glomerulonephritis the lesions are distinctly capillary and vascular. In this form of purpura it seems likely that the lesions develop as a result of a toxic endotheliosis, although this term should not be taken to imply that capillary endothelium, sensitized by the toxin, proliferates as in other forms of endotheliosis.

TABLE 1.—REVIEW OF BLOOD COUNTS IN SCARLATINAL PURPURA *

	Day of disease.	Red cells (mills.).	Hemoglobin, %.	Platelets (thous.).	White cells (thous.).	Neutrophils, %.	Lymphocytes, %.	Monocytes, %.	Myelocytes, %.	Eosinophils, %.	Basophils, %.	Remarks.
Biernacki and Dykes	8th week	3.6	..	....	50.0	85	10	..	..	2		
Elliott	19th day	2.3	..	Not incr.	65.4	79	13	16	5.2	5	..	3 nucleated red cells
Risel	16th day	5.2	..	Not incr.	38.1	83.3	10.4	..	2.1	..	2.1	3 nucleated red cells
Rolleston and McCirick	10th day	1.8	..	Not incr.	57.6	63.4	..	..	6.3	..	..	Many microcytes
McCirick	18th day	3.7	..	Not incr.	15.7	86	..	..	2.5			
Prior	22d day	5.6	..	300	4.0	83	15	1.5	..	0.6	..	Coag. time, 4 mins.
Gibson and Hobson	16th day	4.9	..	Large numbers	27.3	71	21	8				
Wood-Smith	16th day	5.4	80	163	6.4	61	30	8	..	..	1	Platelets, 378,000 3 mos. later
Box and Massingham	13th day	3.4	65	0 in 4000 R.B.C.	39.8	81.5	14	2	2.5			
Prior	23d day	4.5	64	146 (some very large)	21.9	77	L.4 S.11 .5	4	..	3	..	Transitionals, 0.5%
Prendergast	40th day	4.5	55	None seen	20.4	50	32	..	..	2	..	Transitionals 4%
Box	5th week	2.9	40	93	22.1	66	26	6	..	2	..	Few nucleated red cells; polychromasia
Fox and Enser (Case 1)	11th day	4.1	92	367	23.6	78	11	7	3.5	0.5	..	Coag. time, 4 min.; bleed time, 5 min.; sed. rate, normal
Fox and Enser (Case 2)	7th day	2.6	48	154	5.0	56	27	3	5	7	2	Poikilocytosis; anisocytosis; microcytes; bleed. time, 1.5 min.; coag. time, 1 min.

* Most of the data in this table are taken from the article by Box,[3] in which the differential counts did not always add up to 100%.

A study of the reported cases discloses rather incomplete hematologic investigations. Table 1 summarizes the available literature on the subject and includes data from Cases 1 and 2 reported here.

In our cases, thrombocytopenia did not occur. There was a moderate to severe acute anemia, and leukocytosis may occur. The stained smears did not give any evidence of significant bone marrow activity.

Treatment of the condition can hardly be said, at the present time, to be entirely specific or even well-founded. We found transfusions, and, we believe, snake venom to be helpful and perhaps effective. However, spontaneous recovery is also a possibility, particularly in the milder cases. The effectiveness of transfusion is probably based upon a desensitization of the capillary endothelium, or perhaps its past results are due to increase in capillary "resistance." Peck and Schneierson[10] showed that moccasin venom did not prevent the development of nephritis in scarlet fever, but also it did not damage the renal capillaries. Since the glomerulonephritis is essentially a vascular phenomenon, Baehr suggested the use of venom to inhibit the development of the lesion, much in the manner that venom inhibits or prevents the Shwartzman phenomenon. It was from that point of view that the venom was used in this case. The use of venom in purpura has been reported by several authors, notably, Rosenthal and Peck.[9] We hold no brief for the use of venom in these cases, but suggest it be given a trial early in the condition.

Splenectomy has been suggested by several authors, notably, Pemberton,[11] Askey and Toland,[1] Brown and Elliott,[3] and Pollok.[12] Jones and Tocantins[5] suggest the use of whole blood transfusion. Rudisill[13] reports the successful use of Roentgen ray irradiation of the spleen. Klima[6] recommends Tryphman (adrenals); and Greenwald,[4] snake venom. To us splenectomy and irradiation seem decidedly contraindicated.

In the final analysis, this type of purpura appears to be due to an allergic or hypersensitive state to a specific protein agent. Treatment should be directed to minimizing the allergy (increased resistance) or neutralizing the antigen.

Summary. Purpura in severe and mild forms occurs rarely in scarlet fever. Thrombocytopenia does not appear to be a factor in the production of the purpura. Purpura did not occur in the reported cases prior to the scarlet fever. Sensitization of the capillary endothelium by the scarlet fever toxin affords a reasonable explanation for the purpura, since the scarlet fever toxin strongly affects capillary endothelium. Hematuria in scarlet fever, in the absence of other evidence of nephritis, is probably an expression of the effect of the scarlet fever toxin on the glomerular endothelium, and in that sense, is indicative of renal purpura. Hematuria, therefore, is not necessarily evidence of nephritis.

The literature on the subject is reviewed and in this report 4 instances of purpura following non-fatal scarlet fever are described. The postmortem findings in 2 other instances are briefly reviewed.

REFERENCES.

(1.) **Askey, J.**, and **Toland, C.**: Arch. Surg., **23**, 103, 1933. (2.) **Box, C. R.**: Lancet, **1**, 1217, 1933. (3.) **Brown, D.**, and **Elliott, R.**: J. Am. Med. Assn., **107**, 1781, 1936. (4.) **Greenwald, H.**: Am. J. Dis. Child., **49**, 347, 1935. (5.) **Jones, H.**, and **Tocantins, L.**: J. Am. Med. Assn., **100**, 83, 1933. (6.) **Klima, R.**: Klin. Wchnschr., **15**, 935, 1936. (7.) **McConnell, G.**, and **Weaver, H.**: J. Am. Med. Assn., **78**, 165, 1922. (8.) **Peck, S. M.**: J. Immunol., **25**, 447, 1933. (9.) **Peck, S. M.**, and **Rosenthal, N.**: J. Am. Med. Assn., **104**, 1066, 1935. (10.) **Peck, S., Schneierson, S.**, and **Lyttle, J. D.**: Am. J. Dis. Child., **52**, 796, 1936. (11.) **Pemberton, J.**: Am. J. Surg., **24**, 793, 1934. (12.) **Pollok, L. W.**: Ibid., **34**, 340, 1936. (13.) **Rudisill, H.**: J. Am. Med. Assn., **107**, 2119, 1936. (14.) **Smith, L. W.**: Am. J. Path., **12**, 373, 1936. (15.) **Stevenson, E. C.**: Western Med. Rev., **17**, 116, 1912.

CHRONIC LEUKEMIA.

A Study of the Incidence and Factors Influencing the Duration of Life.

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The medical literature contains little data relating to the incidence of leukemia. This study of the records of patients suffering from leukemia in several large general hospitals located in New York, Boston, and Philadelphia* has provided additional information not only with regard to the incidence but also concerning the significance of certain prognostic signs.

The Variation in the Incidence of Leukemia Since 1904. Wollstein and Bartlett[17] (1925) reported 15 instances of acute leukemia among 25,246 admissions to the Babies' Hospital in New York City. Hoffman and Craver[4] (1931) state that myelogenous leukemia makes up only 0.4% of the patients seen at Memorial Hospital in New York City. Ordway and Gorham[12] state that 1 case of leukemia occurs among every 1000 hospital admissions. Ikeda[6] (1931) found 77 cases of leukemia in the records of 12,396 necropsies at the University of Minnesota Hospital from 1900 to 1928 inclusive. Nielsen[11] (1932) reported that in Denmark the annual death rate from leukemia was roughly 1 per 50,000 population, the figure being based on an examination of death certificates for the period 1923–1932. The first two of these reports are not from general hospitals.

The autopsy records of the Boston City, Massachusetts General, and the New York Hospitals from 1905 to 1934 were studied in an effort to determine if there had been any change in incidence during that 30-year period.

* We are grateful to the Boston City, the Children's (Boston), the Massachusetts General, and the University of Pennsylvania Hospitals for permission to make use of their records.

Cases of acute and chronic myelogenous, lymphogenous, and monocytic leukemia were included.* Instances in which the diagnosis was questionable and cases of lymphosarcoma were not included. Because of the fact that at the New York Hospital, autopsies on stillbirths and individuals less than 10 years of age accounted for only 5% of the necropsies prior to 1932 and 50% of the total since 1932, all autopsies on persons 10 years of age and under have been excluded from this hospital's series. The results are presented in Table 1.

TABLE 1.—THE INCIDENCE OF LEUKEMIA—AUTOPSIES.

	Boston City Hospital.		*Mass. Gen. Hospital.*		*New York Hospital.*	
Years.	No. of autopsies.	Cases of leukemia.	No. of autopsies.	Cases of leukemia.	No. of autopsies.	Cases of leukemia.
1925–34	4909	41 (0.8%)	2793	59 (2.0%)	1622	18 (1.1%)
1915–24	1865	10 (0.5%)	1360	19 (1.4%)	915	7 (0.78%)
1905–14	1601	8 (0.5%)	2231	19 (0.9%)	1003	5 (0.5%)
Totals	8375	59	6384	97	3540	30

Although the incidence of leukemia at necropsy differed in the hospitals studied, in each instance both the percentage of leukemia cases and the number of leukemia cases have increased with each succeeding decade. The significance of this increase at autopsy cannot be determined because the result obtained in a study of this kind is affected by so many factors that cannot be measured or estimated accurately, such as the improvement in the diagnosis of leukemia by the practising physician, the percentage of such patients in the community that were hospitalized, the incidence in all the other hospitals in the community during the same period, the policy of the hospital about admitting certain types of disease, the presence or absence of a staff member especially interested in leukemia, the decreasing number of deaths from other causes.

The incidence of leukemia based on clinical diagnoses and hospital admissions at The Children's (Boston), Massachusetts General, and the University of Pennsylvania Hospitals is shown in Table 2. Only the first admission of the leukemia patient was counted. The figures for the different hospitals cannot be compared, because the figure for "number of admissions" does not have the same significance at all the institutions. At the Children's Hospital (Boston) it includes only ward and private medical patients, at the Massachusetts General Hospital only the medical and surgical patients admitted to the public wards, while at the University of Pennsylvania Hospital it includes all admissions on all services, private room, and public ward.

Prognostic Factors. Most writers on the subject[2,7,12,13,16] state that a decline in the general condition of the patient, increasing

* They have been grouped rather than tabulated according to the predominating type of cell because of the relatively small number of cases in most of the periods studied.

anemia, increasing percentage of blast cells, increasing leukocyte count, and the manifestation of a bleeding tendency indicate an unfavorable course and progression of the disease. While the correctness of these prognostic signs in a majority of instances is established by clinical experience, in the literature there are few records of attempts to evaluate the accuracy of these guides by the study of a group of cases. The purpose of the second part of this communication is to present the results of such a study in order to determine the relationship of several of these factors to the duration of life.

TABLE 2.—INCIDENCE OF LEUKEMIA: CLINICAL DIAGNOSES.

Years.	No. of thousand admissions.	No. of leukemia cases.	Leukemia per 1000 admissions. 5-year period.	Leukemia per 1000 admissions. 10-year period.
Children's Hospital, Boston.				
1930–1934	5.52	46	8.3	
1925–1929	4.98	31	6.3	
				7.3
Massachusetts General Hospital.				
1930–1934	38.7	79	2.0	
1925–1929	36.5	43	1.2	
				1.6
1920–1924	32.8	58	1.5	
1915–1919	24.0	15	0.6	
				1.05
University of Pennsylvania Hospital.				
1930–1934	48.6	34	0.64	
1925–1929	49.1	28	0.57	
				0.60
1920–1924	40.1	21	0.52	
1915–1919	20.9	13	0.62	
				0.57

Material. The records of 478 cases of leukemia at The Children's (Boston), Massachusetts General, New York, and the University of Pennsylvania Hospitals have been studied. The great majority of these patients were admitted between the years 1925–1936, the remainder between 1917–1925. In the group of 478, there were 180 cases of chronic myelogenous leukemia and 128 of chronic lymphogenous leukemia. In 87 patients with chronic myelogenous leukemia and 49 patients with chronic lymphogenous leukemia the duration of life after the onset of symptoms apparently due to leukemia is known. These 136 cases form the material for the second part of this communication.

Only cases of chronic leukemia are included in this study. Regardless of the age at onset, no cases with a total duration from the onset of symptoms to death of less than 6 months have been included, and no records of individuals less than 15 years of age at the time of onset have been included. Practically all these patients were treated by irradiation, arsenic, transfusion, or a combination of these agents.

Age Incidence. The age incidence of the 180 individuals with chronic myelogenous leukemia and of the smaller group of 87 in whom the total duration of the disease is known was similar to that reported by Ward,[15] 1917 (247 cases), Minot, Buckman and Isaacs,[10] 1924 (166 cases), Hoffman and Craver,[4] 1931 (80 cases), and Rosen-

thal and Harris,[14] 1935 (104 cases), the greatest number occurring between the ages of 35 and 45.

The age incidence of the 128 patients with chronic lymphogenous leukemia, and the smaller group of 49 considered in more detail, was similar to that reported by Ward,[15] 1917 (84 cases), Minot and Isaacs,[9] 1924 (92 cases), and Rosenthal and Harris,[14] 1935 (104 cases), the greatest number occurring between the ages of 45 and 55.

Sex Incidence. Of the 180 cases of chronic myelogenous leukemia, 108 (60%) were males and 72 (40%) were females. Of the 87 patients in whom the total duration of the disease is known, 46 (53%) were males and 41 (47%) were females. Minot, Buckman and Isaacs,[10] 1924, found that in 605 cases, including their own and those reported by Cabot, Vogel, Ward, Giffen and Lazarus, 60% were males and 40% were females. In Hoffman's and Craver's series of 82 cases,[4] 1931, 68% were males and 32% were females.

Of the 128 individuals in this series having chronic lymphogenous leukemia, 72% were males and 28% were females. Of the 49 in whom the total duration of the disease is known, 36 (72%) were males and 13 (28%) were females. Ward,[15] 1917, reported that 75% of 84 cases of chronic lymphogenous leukemia were males and Minot and Isaacs,[9] 1924, reported that 74% of 92 cases were males.

Duration of Life. Minot, Buckman, and Isaacs[10] (1924) found the average duration of life after onset of symptoms to be 3.5 years in 78 patients with chronic myelogenous leukemia treated by irradiation, 3.04 years in 52 patients not treated by irradiation. About 10% died in the first year, 42% lived from 2 to 4 years, and 12% survived more than 5 years. Hoffman and Craver[4] (1931) found the average duration of life after onset of symptoms to be 3.36 years in 71 patients with chronic myelogenous leukemia treated by irradiation. Arendt and Gloor[1] (1932) reported that the average duration of life after onset of symptoms was slightly over 4 years in their 39 patients with chronic myelogenous leukemia treated by Roentgen ray and arsenic. Rosenthal and Harris[14] (1935) reported that of 157 patients with chronic myelogenous leukemia, 35% died between the fourth and twelfth month, 45% lived from 2 to 4 years, a few survived from 5 to 11 years. In 104 cases of chronic lymphogenous leukemia they found the duration of life to be essentially the same. Minot and Isaacs[9] (1924) found the average duration of life after onset of symptoms in 80 patients with chronic lymphogenous leukemia over 30 years of age to be 3.45 years, the average being the same in irradiated and non-irradiated patients. About 60% lived from 1 to 4 years, 14% from 6 to 8 years.

Chart 1 represents the percentage of the present series surviving at each year after onset. The average duration of life after onset of symptoms was 3.2 years for the group with chronic myelogenous leukemia and 3.6 years for the group with chronic lymphogenous

leukemia. The individual variations were from 6 months to 16 years in each type.

Although this series of 87 cases of chronic myelogenous leukemia and 49 cases of chronic lymphogenous leukemia is a small one, because the age distribution, sex distribution, and duration of life are the same as those reported in much larger series, this group is thought to be a typical one.

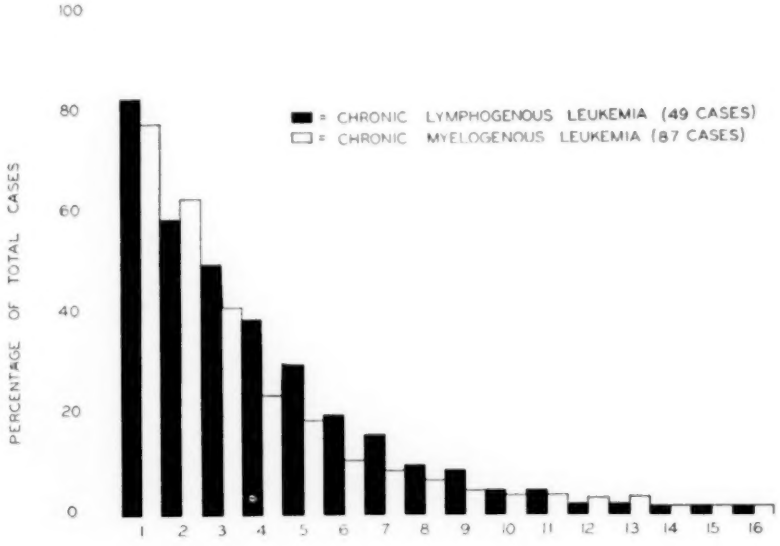

CHART I - DURATION OF LIFE AFTER ONSET OF SYMPTOMS (YEARS)

Relation of Age at Onset to Duration of Life. Minot, Buckman and Isaacs[10] (1924) and Hoffman and Craver[4] (1931) thought that the age at which chronic myelogenous leukemia appeared did not greatly influence its duration. Minot and Isaacs[9] (1924) stated that chronic lymphogenous leukemia lasted a shorter time in younger persons than in older persons, but their series included only 7 individuals less than 30 years of age.

Table 3 gives information concerning the duration of life after the onset of symptoms in the two type of cases in this series. The age groups that vary from the average of the entire group with chronic myelogenous leukemia are the young and old, but there are probably too few cases for the results to be significant. Individuals developing symptoms from lymphogenous leukemia between the ages of 40 and 60 averaged a longer course than the others.

Relation of Anemia to the Duration of Life. Marked anemia or increasing anemia is accepted generally as an unfavorable sign. Forkner,[2] Whitby and Britton,[16] Kracke and Garver,[7] Pepper and

Farley.[13] Well recognized but little emphasized is the difference of the significance of anemia in the two types of leukemia under consideration. Minot and Isaacs[9] (1924) state that in cases of chronic lymphogenous leukemia with hemoglobin of 50% or below, it is rare to see much symptomatic improvement as the result of therapy in contrast to the distinct benefit often seen in cases of chronic myelogenous leukemia having marked reduction in hemoglobin. Forkner[2] states that severe anemia is more serious in patients with chronic lymphogenous leukemia than in those with chronic myelogenous leukemia.

TABLE 3.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA, AGE OF ONSET OF SYMPTOMS, AND AVERAGE DURATION OF LIFE AFTER ONSET OF SYMPTOMS.

Chronic myelogenous leukemia.			Chronic lymphogenous leukemia.	
Average duration of life (yrs.).	No. of cases.	Age by decades.	Average duration of life (yrs.).	No. of cases.
1.0	2	10–19	1.0	2
1.5	9	20–29	3.0	3
4.4 *3.3	25 *21	30–39	3.0	4
3.3	23	40–49	4.5	9
3.0	20	50–59	4.5	19
3.3	6	60–69	2.1	11
0.7	2	70–79	4.0	1
3.2	87	Totals	3.6	49

* Excluding the 4 cases living more than 10 years, all of which occurred in this decade.

In this series, cases of both types of leukemia have been divided into three groups, those surviving less than 1 year, those surviving 1 to 3 years, and those surviving more than 3 years. They also have been divided into three groups according to the degree of anemia: those with marked anemia (hemoglobin less than 50%), those with moderate anemia (hemoglobin 50 to 70%), and those with little or no anemia (hemoglobin over 70%). Hemoglobin values are those before treatment was given. They are recorded in per cent because factors for conversion into grams were not available in every instance and, even with slightly different standards, percentage values were considered satisfactory for the divisions employed. The duration of life is that after the hemoglobin determination and not after the onset of symptoms. This way of stating the duration of life was selected because this study is concerned mainly with the duration of life after the patient first consults a physician, and because only in exceptional instances could one learn the hemoglobin value at the time symptoms developed. The results are presented in Table 4.

In this series, the groups with marked anemia had a much shorter course than the other groups, and this was especially evident in

those with lymphogenous leukemia. No patient with either type of leukemia and a hemoglobin of 30% or less (12 cases) survived for as long as a year. That a marked anemia does not invariably indicate an unusually short course is shown by the fact that of the 35 patients with chronic myelogenous leukemia who had hemoglobin values of between 30 and 50%, 12 survived for more than 1 year, 3 for more than 3 years. One patient with chronic lymphogenous leukemia who had a hemoglobin reading of 45% lived for 16 years after coming under observation.

TABLE 4.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA. HEMOGLOBIN (%) AND PERIOD OF SURVIVAL.

Chronic Myelogenous Leukemia.

Initial hemoglobin (%).	No. of cases living less than 1 year.	No. of cases living 1–3 years.	No. of cases living more than 3 years.	Totals.
20–49	23	9	3	35
50–69	16	16	6	38
70–100	2	5	7	14
Totals	41	30	16	87

Chronic Lymphogenous Leukemia.

20–49	12	0	1	13
50–69	8	6	1	15
70–100	8	7	6	21
Totals	28	13	8	49

Relation of Leukocyte Count to Duration of Life. The total leukocyte count is considered one of the less reliable prognostic signs. Its tendency in some patients to rise abruptly and in others to drop steadily just before death is well known. That in some instances it varies greatly and in others only slightly, with and without treatment, and frequently fails to parallel the clinical course of the patient is also well known. These are probably some of the factors responsible for the different opinions that have been expressed regarding its interpretation.

Kracke and Garver[7] (1937) quote Naegeli as saying that patients with chronic myelogenous leukemia and high leukocyte counts succumb earlier than those with low leukocyte counts. With reference to lymphogenous leukemia, they state that the higher the leukocyte count the more unfavorable the prognosis. Rosenthal and Harris[14] (1935) found that the majority of their patients with chronic myelogenous leukemia with leukocyte counts of 15,000 per c.mm. or less died within 1 year. Hunter[5] (1937) states that patients with chronic myelogenous leukemia and low leukocyte counts have a more rapid course than those with higher counts.

Cases of both types of leukemia in the present series are tabulated according to periods of survival and total leukocyte counts as shown in Table 5. The leukocyte count in each instance is the initial

count before treatment, the period of survival is that after the leukocyte count, not after the onset of symptoms.

TABLE 5.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA: LEUKOCYTE COUNT AND PERIOD OF SURVIVAL.

Initial leukocyte count.	No. of cases living less than 1 year.	No. of cases living 1–3 years.	No. of cases living more than 3 years.	Total.
Chronic Myelogenous Leukemia.				
3,000–39,000	15	0	1	16
40,000–300,000	15	19	13	47
301,000–750,000	11	11	2	24
Totals	41	30	16	87
Chronic Lymphogenous Leukemia.				
3,000–39,000	11	5	5	21
40,000–300,000	13	5	3	21
301,000–750,000	4	3	0	7
Totals	28	13	8	49

In this series, the group of patients having myelogenous leukemia and a leukocyte count of less than 40,000 per c.mm. had a much shorter course than the other groups. A relatively low leukocyte count was a more reliable sign of an early fatal outcome than a high leukocyte count was of a more favorable outlook. Of the 16 patients with myelogenous leukemia having leukocyte counts of less than 40,000 per c.mm., 13 had hemoglobin values of less than 50%: not one of these 13 individuals survived for as long as 1 year. The group with chronic lymphogenous leukemia having lower counts fared slightly better than the groups with the higher counts.

In view of the decrease in leukocyte count that usually accompanies improvement during therapy, it was somewhat surprising to find that in this series the untreated patients with myelogenous leukemia having lower leukocyte counts apparently lived a shorter time than those with higher counts. Other explanations for the difference in the expectancy of life after diagnosis were considered. One possibility is that the small group of patients with the lower leukocyte counts might have had symptoms for a longer time before consulting a physician than those with higher counts.

The average duration of symptoms before and after diagnosis in the patients with myelogenous leukemia having counts less than 40,000 per c.mm. and in those with higher counts is shown in Table 6. That average values are misleading in this instance is shown by the fact that of the group of 16 with leukocyte counts of less than 40,000 per c.mm. only 1 individual lived even half as long after diagnosis as the average duration of life after diagnosis for the whole group. If the rare cases living more than 10 years are excluded from each group as shown in the second half of the table, the average duration of life after coming under observation is 0.7 years for the 15 cases with leukocyte counts of less than 40,000 per c.mm. and 1.4 years for

the 67 cases with higher leukocyte counts. The average duration of life after the onset of symptoms in the group with lower leukocyte counts is only 0.4 years less than the group with higher counts as the former apparently came under observation 0.3 years later in the course of the disease.

TABLE 6.—CHRONIC MYELOGENOUS LEUKEMIA: LEUKOCYTE COUNT AND DURATION OF DISEASE BEFORE AND AFTER DIAGNOSIS.

All Cases.

Initial leukocyte count.	Average duration of life (yrs.).	Average duration of symptoms before diagnosis (yrs.).	Average duration of life after diagnosis (yrs.).	No. of cases.
Less than 40,000	3.2	1.3	1.9	16
More than 40,000	3.2	1.45	1.75	71
Cases Living Less Than 10 Years.				
Less than 40,000	2.0	1.3	0.7	15
More than 40,000	2.4	1.0	1.4	67

Relation of Bleeding Manifestations to the Duration of Life. Bleeding is one of the commonest manifestations of leukemia. That it occurs most frequently in advanced and acute cases and is a sign of an early termination of the disease is accepted generally.

Minot and Buckman[8] (1924), in studying the course of the platelet count in 75 patients with chronic myelogenous leukemia and 50 patients with chronic lymphogenous leukemia, observed petechiæ in 50% of those with myelogenous leukemia. The petechiæ were always associated with thrombocytopenia, usually appeared towards the end of the disease, occasionally a few years before death. Evidence of bleeding other than petechiæ occurred in 25% of the patients. In chronic lymphogenous leukemia, bleeding in the form of ecchymoses and petechiæ was more common than in chronic myelogenous leukemia. Usually the bleeding was present only shortly before death. In 10%, however, it was found for as long as 1 year before death and sometimes for 2 years.

At the time of the first admission, a history of purpura, bleeding gums, epistaxis, hematemesis, melena, occurring alone or in combination was obtained in 18 (20%) of 87 patients with chronic myelogenous leukemia and in 8 (16%) of 49 patients with chronic lymphogenous leukemia. Of these 18 patients with myelogenous leukemia, 12 (66%) succumbed within 1 year after the appearance of bleeding, while with the 69 individuals with myelogenous leukemia giving no history of bleeding 29 (43%) died during the first year. Some of the patients included in the group of 69 developed bleeding before death, but in the study only the findings at the first visit were considered. Of the 6 patients with myelogenous leukemia giving a history of bleeding who survived for more than 1 year, 3 had hemoglobin values of less than 50%, all had leukocyte counts between 60,000 and 770,000 per c.mm., while of the 12 dying during

the first year, 9 had hemoglobin values of less than 50%, 9 had leukocyte counts of less than 40,000 per c.mm. Six individuals not included in the group of 18 patients with myelogenous leukemia and bleeding gave histories of excessive vaginal bleeding; all 6 survived more than 1 year, 3 for more than 3 years.

Of 8 subjects with lymphogenous leukemia giving a history of bleeding, 4 died during the first year, 4 lived from 1 to 2 years, none survived longer than 2 years. The number of cases is too small for the result to be significant.

The group of patients with chronic myelogenous leukemia with evidence of bleeding lived a shorter time after coming under observation than the group without bleeding. That some patients with myelogenous leukemia with bleeding manifestations may do well under treatment is shown by the survival of 4 individuals for more than 3 years. This improvement is less likely to occur if there is marked anemia, and rarely occurs if the leukocyte count is low.

Relation of Specific Skin Lesions to Prognosis. Specific lesions of the skin were proved by biopsy or autopsy in 9 of the 128 cases of chronic lymphogenous leukemia, in 1 of the 180 cases of chronic myelogenous leukemia. The average duration of life after the onset of symptoms in the 9 cases of lymphogenous leukemia with specific skin lesions was 3.5 years as compared with 3.45 years for the whole group of 49. The average duration of life after diagnosis was 1.0 year in the 9 cases with skin lesions and 1.6 years in the 40 cases without skin lesions. Only 1 case with skin lesions had a hemoglobin of less than 50%, all 9 had leukocyte counts between 55,000 and 600,000 per c.mm., 8 being over 90,000 per c.mm.

The duration of life in the individual with myelogenous leukemia and specific skin lesions is not known. Goldhamer and Barney[3] (1936), reviewing 16 previously reported cases of myelogenous leukemia with skin manifestations and 1 of their own, found the duration of life after the appearance of skin lesions to vary from 11 days to 4 months, the average being 64 days.

Comment. In determining the incidence of leukemia, the acute leukemias and the different cell types were not grouped separately because in each period studied the total number of cases was so small that further subdivision seemed inadvisable.

A consideration of the relationship of the immature types of cells to the duration of life has not been included because different persons made the counts and used different classifications. Therefore, any conclusion that one might reach would not be justified. Basal metabolic rates, platelet counts, and values of the various clotting factors were not included because of insufficient data.

No conclusions could be drawn as to the benefit derived from transfusions in this series. In most instances, they were given to patients apparently in the advanced stages of the disease, having a poor immediate prognosis.

Discussion of the factors responsible for the anemia, bleeding, and variations in the leukocyte count is beyond the scope of this paper.

The prognostic factors considered are those that were present when the patient was first seen, and should enable one to give a more reliable estimation of the duration of life in certain types of cases. The subsequent course of the patient while under treatment is, of course, valuable in this estimation. The results also demonstrate that those individuals in whom the duration of the disease will be short are recognized more easily than those who will have the average duration of life or better, but that in exceptional instances a combination of unfavorable signs may be misleading.

In general, the results of the study confirm the prevailing clinical impression.

Summary and Conclusions. 1. The incidence of leukemia as determined from clinical records was 7.3 cases per 1000 admissions at the Children's Hospital, Boston, for the years 1925–1934. At the Massachusetts General Hospital there were 1.05 cases of leukemia per 1000 admissions for the period from 1915–1924, 1.6 cases per 1000 admissions from 1925–1934. At the University of Pennsylvania Hospital there were 0.57 cases of leukemia per 1000 admissions from 1915–1924, 0.60 cases per 1000 from 1925–1934.

2. The incidence of leukemia at autopsy at the Boston City Hospital, Massachusetts General Hospital, and the New York Hospital, was 0.8%, 2.0%, and 1.1% respectively for the period 1925–1934. This is an increase of from 60 to 100% over the 1905–1915 period in each institution.

3. Because of reasons discussed, it cannot be concluded that the apparent increase in incidence is significant.

4. The average duration of life after onset of symptoms was 3.2 years in 87 patients with chronic myelogenous leukemia and 3.6 years in 49 patients with chronic lymphogenous leukemia. About 80% survived for 1 year, 40% for 3 years, 20% for 5 years, and 4% for 10 years or more. Autopsies were performed on only 60% of this series.

5. In this series of 87 patients which chronic myelogenous leukemia, the duration of life was shorter in the individuals having marked anemia, relatively low leukocyte counts, or evidence of bleeding before treatment was given than in those without these features. If more than one of these findings were present, the probability of an early fatal outcome was greater than if only one was present.

6. The patients with chronic lymphogenous leukemia having marked anemia had a shorter course than those with little or no anemia. The duration of life was slightly longer in individuals having relatively low leukocyte counts than in those with higher counts.

7. The duration of life after the onset of symptoms in 9 patients with chronic lymphogenous leukemia possessing specific skin lesions did not differ from those without specific skin lesions.

REFERENCES.

(1.) **Arendt, J.**, and **Gloor, W.**: Strahlentherapie, **44**, 715, 1932. (2.) **Forkner, C.**: Leukemia, Nelson's New Loose-Leaf Medicine, New York, T. Nelson and Sons, **4**, 67, 1937. (3.) **Goldhamer, S. M.**, and **Barney, B. F.**: J. Am. Med. Assn., **107**, 1041, 1936. (4.) **Hoffman, W. J.**, and **Craver, L. F.**: Ibid., **97**, 836, 1931. (5.) **Hunter, F. T.**: Med. Clin. North America, **21**, 349, 1937. (6.) **Ikeda, K.**: Am. J. Clin. Path., **1**, 167, 1931. (7.) **Kracke, R.**, and **Garver, H.**: Diseases of the Blood and Atlas of Hematology, Philadelphia, J. B. Lippincott & Co., Chap. 25 and 26, 1937. (8.) **Minot, G. R.**, and **Buckman, T. E.**: Am. J. Med. Sci., **169**, 477, 1925. (9.) **Minot, G. R.**, and **Isaacs, R.**: Boston Med. and Surg. J., **191**, 1, 1924. (10.) **Minot, G. R.**, **Buckman, T. E.**, and **Isaacs, R.**: J. Am. Med. Assn., **82**, 1489, 1924. (11.) **Nielsen, J.**: Acta Radiologica, **13**, 385, 1932. (12.) **Ordway, T.**, and **Gorham, L. W.**: The Leukemias, Cecil's Text-book of Medicine, 2d ed., Philadelphia, W. B. Saunders Company, p. 976, 1931. (13.) **Pepper, O. H. P.**, and **Farley, D. L.**: Practical Hematological Diagnosis, Philadelphia, W. B. Saunders Company, Chap. 11, 1933. (14.) **Rosenthal, N.**, and **Harris, W.**: J. Am. Med. Assn., **104**, 702, 1935. (15.) **Ward, G.**: Brit. J. Child. Dis., **14**, 10, 1917. (16.) **Whitby, L. E. H.**, and **Britton, C. J. C.**: Disorders of the Blood, 2d ed., Philadelphia, P. Blakiston's Son & Co., Inc., Chap. 18, 1937. (17.) **Wollstein, M.**, and **Bartlett, F. H.**: Am. J. Med. Sci., **169**, 819, 1925.

FAILURE OF ELECTROMAGNETICALLY INDUCED HEAT TO INCREASE RENAL EFFICIENCY.

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Diathermy treatment over the kidneys has been shown[11] to produce no significant change in renal function as measured by urea clearance or in arterial blood pressure. Heating of internal organs by means of electromagnetic induction ("inductotherm") is believed to produce much higher temperatures in them.[3,4,9] By this method greater heat is generated in the more conductive, that is, the more vascular tissues, and less in such tissues as skin, fat and bone.

Application of heat to an organ is generally thought to increase the flow of blood through it. It was, therefore, reasonable to believe that inductotherm treatment of the kidneys might increase the blood flow to them and that this might be demonstrated by means of urea and creatinine clearances.[8,12] Although it has been shown that these two clearances generally parallel one another,[1,2,5,7,13] it was possible that treatment might affect the two tests in a different manner indicating change in the normal relationship of glomerular and tubular activity. For this reason both tests were made.

TABLE 1.—ANALYSIS OF DATA.

Case No.	Date.	Hour.	Urine volume, cc./min.	Blood urea nitrogen, mg./100 cc.	Urea clearance, % of normal.	Creatinine clearance, % of normal.	Blood pressure.	Temp., ° F.	Diagnosis.
	1937.								
1	12/6	1st	6.68	11.5	44.9	.....	146/90	....	Acute nephritis
		*2d	1.35	11.5	32.7†	.....	136/76	100.2	
		3d	4.8	11.5	40.2	.....	138/82	99.8	
							144/90	99.6	
	12/7	1st	9.5	10.5	52.1	.....	136/80	98.4	
		*2d	5.29	9.3	47.2	.....	128/72	99.4	
		3d	4.91	10.5	40.6	.....	124/76	99.4	
							134/88	99.0	
	12/20	1st	3.38	14.2	56.8	52.6	104/62	98.6	
		*2d	6.42	12.7	59.6	51.2	106/60	99.0	
		3d	7.66	13.0	54.3	52.6	106/68	98.6	
		4th	8.04	13.0	52.3	48.2	....	98.6	
		5th	5.66	12.3	45.6	41.2	106/68	98.6	
	12/30	1st	3.72	11.8	53.5	58.8	112/80	98.6	
		‡2d and 3d	3.35	11.8	44.4	46.5	120/38	101.2	
		*4th	0.333	11.8	26.6†	20.7	112/50	103.4	
		5th and 6th	2.50	11.8	21.7	23.1	120/76	101.0	
		7th	4.34	10.9	28.2	32.5	110/54	99.2	
2	12/17	1st	3.56	15.9	68.0	.....	98/54	98.4	Acute nephritis
		*2d	6.03	15.7	84.1	.....	88/20	98.4	
		3d	5.95	15.0	70.4	.....	108/52	98.4	
		4th	6.82	15.9	73.5	.....	100/68	98.2	
		5th	7.0	15.0	78.2	.....	....	98.8	
3	12/8	1st	1.0	90.5	10.6†	.....	176/110	100.6	Chronic nephritis
		*2d	1.05	94.1	11.4†	.....	170/106	101.6	
		3d	1.23	95.6	11.3†	.....	174/108	100.4	
		4th	0.86	93.5	9.5†	.....	188/120	100.4	
	12/21	1st	0.40	110.0	6.0†	5.7	190/96	102.4	
		*2d	0.47	116.0	6.4†	5.3	194/94	104.4	
		3d	0.38	106.0	5.1†	6.1	196/94	104.2	
		4th	0.5	113.0	5.8†	8.0	....	103.0	
		5th	0.31	109.5	5.3†	5.2	....	102.6	
4	12/23	1st	1.81	101.0	8.1†	6.5	174/94	98.6	Chronic nephritis
		*2d	1.62	100.2	9.2†	6.9	168/82	99.0	
		3d	1.83	91.8	9.4†	8.1	168/90	97.6	
		4th	1.50	94.0	8.8†	6.5	....	98.0	
		5th	1.96	96.0	10.0†	8.4	....	98.0	
	12/28	1st	2.22	65.6	12.4	14.1	176/100	98.4	
		*2d	2.44	67.8	12.2	16.5	182/86	98.6	
		3d	2.70	60.7	13.4	13.8	184/96	98.4	
		4th	2.20	66.4	10.5	12.5	185/94	98.6	
		5th	2.55	65.0	14.7	15.9	....	98.4	
5	12/16	1st	1.46	9.1	56.6†	65.5	174/120	98.4	Hypertension
		*2d	5.04	9.5	55.6	54.6	168/90	98.6	
		3d	3.80	8.6	33.4	36.1	168/120	98.8	
		4th	7.92	8.1	66.9	86.6	162/114	98.8	
		5th	6.57	8.1	64.1	73.0	180/122	98.4	
	12/27	1st	9.15	10.4	64.5	63.1	182/114	98.4	
		‡2d and 3d	4.02	9.4	40.6	43.9	182/112	101.0	
		*4th	0.63	10.9	23.8†	28.8†	138/84	103.4	
		5th	1.05	11.3	39.0†	60.0†	164/110	102.6	
		6th	2.57	10.9	46.7	68.8	158/100	100.8	
		7th	1.83	10.6	28.3†	46.6†	156/110	98.6	
6	12/10	1st	5.34	10.0	79.1	58.8	158/112	97.8	Hypertension
		*2d	7.53	9.5	58.5	52.2	160/112	98.8	
		3d	5.2	9.5	74.1	68.0	180/130	98.2	
		4th	6.0	9.1	47.2	49.7	176/124	97.8	
		5th	9.5	8.6	74.6	66.4	....	98.0	
7	12/15	1st	3.46	14.5	84.6	116.0	158/90	98.2	Pernicious anemia with hypertension
		*2d	6.26	14.1	79.6	92.1	146/74	99.2	
		3d	7.38	13.3	112.0	128.0	170/88	98.6	
		4th	4.46	13.3	78.9	103.0	164/94	98.0	
		5th	7.31	12.6	75.3	99.4	176/90	97.8	
8	12/29	1st	1.83	9.0	96.5†	105.0†	208/110	98.6	Hypertension
		*2d	1.34	9.0	95.6†	99.1†	176/100	99.4	
		3d	2.07	9.4	90.0	98.8	172/102	98.6	
		4th	6.04	9.9	101.5	116.6	174/100	98.6	
		5th	4.30	9.7	93.0	97.6	....	98.4	
9	12/22	1st	7.46	11.8	66.0	64.1	192/102	98.6	Hypertension
		*2d	4.43	11.3	61.1	71.4	186/108	100.4	
		3d	5.26	10.6	59.1	58.5	190/104	99.6	
		4th	10.85	10.1	80.3	81.8	212/114	99.6	
		5th	5.37	10.1	61.4	60.6	192/104	99.0	
10	12/9	1st	6.0	16.2	115.0	.....	105/66	98.4	Rheumatic fever (acute)
		*2d	4.58	15.7	81.6	.....	100/60	99.0	
		3d	1.83	15.0	76.1†	.....	104/64	98.8	
		4th	8.46	14.1	111.2	.....	....	98.2	
		5th	7.22	13.8	110.2	.....	116/70	99.2	

* Inductotherm. † Standard clearance. ‡ Patient wrapped in blankets and inductotherm applied.

Methods. Urea clearances were ascertained by the method of Möller, McIntosh and Van Slyke[10] and creatinine clearance by a modification of the method of Hanzal and Hayman.[6] Following a control period during which clearances were determined, a large disk electrode of the inductotherm was applied over the region of the kidneys with the patient lying on his side. The intensity of the inductotherm was set at maximum and the treatment lasted 1 hour.

No attempt was made in most of the experiments to retain heat in the patient's body. Two patients (Cases 1 and 5) were wrapped in blankets and covered with a rubber sheet during application of the inductotherm to determine the effect of heat retention by the body on the kidneys.

Ten patients were studied, 2 with acute nephritis, 2 with chronic nephritis, 5 with essential hypertension, and 1 with acute rheumatic fever.

Results. When no precaution was taken to prevent dissipation of heat from the rest of the body the rectal temperature rose from 1 to 1½°, except in 1 (Case 3) where fever was already present. When this loss of heat was prevented by blankets the temperature rose to levels of 103° (oral).

During the period of heat treatment or in the periods following it, a moderate decrease in urea clearance occurred in 11 of 16 experiments (Table 1). The most marked decreases were observed when loss of body heat was prevented by means of blankets (Cases 1 and 5). When the renal efficiency was low, as in the 2 patients (Cases 3 and 4) suffering from chronic nephritis, no change in urea clearance was found. This is in agreement with many observations which indicate that the flexibility of response is lost when renal function is seriously impaired by chronic nephritis.

Creatinine clearances usually paralleled the urea clearances. Blood urea was unchanged as the result of heat treatment and urine volume varied irregularly. One patient (Case 3) who had marked edema showed no diuretic response after heat was applied.

It was hoped that heating the kidneys might cause relaxation of hypertonic arterioles, if such existed, in the kidneys of patients with early essential hypertension. If better perfusion of the kidneys with blood occurred, it was possible that arterial blood pressure might fall. Our results show, however, that neither was increased perfusion evident from the clearances nor was there more than slight fall in diastolic blood pressure.

The results of the clearances suggest that, even though heat is induced within the kidneys, dissipation to other parts of the body by the blood causes sufficient somatic vascular dilatation to decrease rather than increase the flow of blood to the kidneys.

Summary. Application of heat produced by electromagnetic induction ("inductotherm") to the region of the kidneys was attempted in patients suffering from acute and chronic nephritis, early essential hypertension and acute rheumatic fever. A slight decrease in renal efficiency as measured by urea and creatinine clearances was observed as a result in this experiment. As these clearances are a rough measure of renal blood flow, heat treatment

reduces rather than increases the flow of blood to the kidneys, possibly by producing vasodilatation in other parts of the body.

Diastolic blood pressure was moderately reduced while heat was being applied but quickly rose to its original level on discontinuing it.

We are indebted to Dr. George W. Stark of Syracuse, N. Y., for the suggestion that inductotherm heating might affect the efficiency of the kidneys, and to the General Electric Company for the loan of the inductothermy apparatus.

REFERENCES.

(1.) **Bing, J.**, and **Bjering, T.**: Acta Med. Scandin., **93**, 318, 1937. (2.) **Cope, C. L.**: Quart. J. Med., **24**, 567, 1931. (3.) **Coulter, J. S.**, and **Osborne, S. L.**: Arch. Phys. Ther., **18**, 135, 1936. (4.) **Dark, E. P.**: Med. J. Australia, **2**, 397, 1936. (5.) **Ellis, L. B.**, and **Weiss, S.**: Am. J. Med. Sci., **186**, 242, 1933. (6.) **Hanzal, R. F.**, and **Hayman, J. M., Jr.**: Proc. Soc. Exp. Biol. and Med., **31**, 730, 1934. (7.) **Hayman, J. M., Jr., Halsted, J. A.**, and **Seyler, L. E.**: J. Clin. Invest., **12**, 861, 1933. (8.) **Mason, M. F., Blalock, A.**, and **Harrison, T. R.**: Am. J. Physiol., **118** 667, 1937. (9.) **Merriman, J. R., Holmquest, H. J.**, and **Osborne, S. L.**: Am. J. Med. Sci., **187**, 677, 1934. (10.) **Möller, E., McIntosh, J. F.**, and **Van Slyke, D. D.**: J. Clin. Invest., **6**, 427, 1928. (11.) **Page, I. H.**: J. Am. Med. Assn., **102**, 1131, 1934. (12.) **Van Slyke, D. D., Rhoads, C. P., Hiller, A.**, and **Alving, A.**: Am. J. Physiol., **109**, 336, 1934. (13.) **Winkler, A. W.**, and **Parra, J.**: J. Clin. Invest., **16**, 859, 869, 1937.

CHEMOTHERAPY OF TYPES VII AND III PNEUMOCOCCAL INFECTIONS WITH SULPHANILAMIDE, 4,4′-DI-(ACETYL-AMINO)-DIPHENYLSULPHONE AND 4,4′-DIAMINO-BENZENESULPHONANILIDE.

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Since the almost simultaneous publications by Rosenthal[13] and by Cooper, Gross and Mellon,[6] both of the above groups [2,3,4a,b,8a,b,13b,14] as well as a number of other investigators[7,10,11,15,16] have reported successful chemotherapeutic experiments with sulphanilamide or other sulphur-containing aromatic compounds in infections caused by pneumococci.

While it is recognized that this chemotherapeutic activity is fractional in degree when compared with that exhibited by these compounds against streptococcal or meningococcal infections, nevertheless their therapeutic action is undeniable and has been confirmed clinically.[1,9,12] Up to the present time these drugs have

been found effective in mice, rats and rabbits and against Types I, II, III, and XIV pneumococci.*

In this paper we are reporting results obtained by the use of two relatively new compounds† in experimental infections caused by Types VII and III pneumococci. One of these compounds, 4,4′-diaminobenzenesulphonanilide, was first used by Whitby[1,6] and later by Bauer and Rosenthal[2]. The former reported this drug to be more effective than sulphanilamide against Type I pneumococcal infections of mice, whereas the latter authors found it "inferior to sulphanilamide against pneumococci." Fourneau and coworkers[7] first investigated the activity of 4,4′-di-(acetylamino)-diphenylsulphone and estimated that 1 mg. produced as much therapeutic effect as 10 mg. of sulphanilamide in pneumococcal infections. This compound was later investigated by Bauer and Rosenthal[2] who also found its antipneumococcal activity superior to that of sulphanilamide.

Method. Groups of 30 to 40 mice or rats were inoculated with suitable dilutions of 18-hour broth cultures and treated orally 3 to 5 hours later with 5 to 12.5% suspensions of the various drugs (Figs. 1 and 2). Since different subcultures of stock strains were used for the several dilutions, the magnitude of the inocula was more relative than absolute.

In light of previous reports of the therapeutic superiority of the sulphone, it was assayed against $2\frac{1}{2}$ times the quantity of sulphanilamide in Exp. 1 A; against 2 times the quantity in Exp. 1 B and 1 C; and against equal amounts in Exp. 1 D.

Results. *Type VII, Mice. A.* (Fig. 1): While 70% of the controls died, the sulphone-treated mice showed a 30% (3 out of 10) mortality rate; and those treated with sulphanilamide, 10% (1 out of 10).

B. (Fig. 1): With treatment continued for only 4 days, there were 7 deaths out of 10 mice treated with the sulphone and 4 deaths out of 10 mice treated with sulphanilamide, contrasted with the 90% death rate in the control group.

C. (Fig. 1): Of 11 mice treated daily for 9 days with sulphanilamide, 7 died; of 11 mice similarly treated with the sulphone, 5 died; and of 10 mice treated with the anilide only 4 died. The control group had a 91% fatality.

D. With the inoculum administered intraperitoneally all controls died in less than 48 hours. The group treated with sulphanilamide had 4 deaths out of 10; that treated with the sulphone, 7 out of 10; and the group treated with the anilide, 8 out of 10.

Type III, Mice and Rats. A. (Fig. 2): With a heavy infecting dose of over 100 M.L.D., poor therapeutic results were obtained.

* While this paper was in press L. E. H. Whitby (Lancet, **1**, 1210, 1938) reported excellent results against Types I, II, III, V, VII, and VIII pneumococcal infections in mice with the sulphonamide compound 2-(p-aminobenzenesulphonamido) pyridine.

† Supplied through the courtesy of the Monsanto Chemical Company, St. Louis, Mo. The sulphanilamide was furnished by E. R. Squibb & Sons, New York City.

All controls died in less than 3 days. The treated groups showed the following fatality rates: the anilide group, 5 out of 10; the sulphanilamide group, 7 out of 10; and the sulphone group, 10 out of 10.

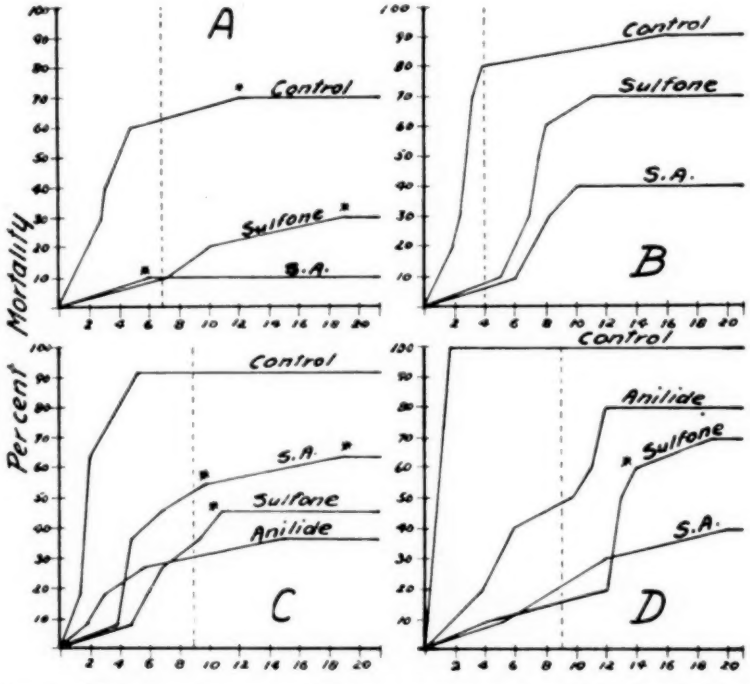

FIG. 1.—MORTALITY CURVES OF MICE INFECTED WITH TYPE VII PNEUMOCOCCUS (ENRICAS†).

Animals infected with diluted 18-hour broth cultures and treated orally each day. Treatment was begun 3 hours after infection and was terminated as indicated by the vertical broken line.

A. Infection: 0.5 cc. of a 10^{-8} dilution in broth, subcutaneously. *Treatment:* Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 10 mg. *B. Infection:* 0.5 cc. of a 10^{-8} dilution in broth, subcutaneously. *Treatment:* Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 10 mg. Sulphone: 10 mice, 5 mg. *C. Infection:* 0.5 cc. of a 10^{-4} dilution in broth, subcutaneously. *Treatment:* Controls: 11 mice, no treatment. Sulphanilamide: 11 mice, 10 mg. Sulphone: 11 mice, 5 mg. Anilide: 11 mice, 10 mg. *D. Infection:* 0.5 cc. of a 10^{-4} dilution in broth, intraperitoneally. *Treatment:* Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 25 mg. Anilide: 10 mice, 25 mg.

* Deaths not due to pneumococcus.

† Obtained from New York City Dept. of Health, 16th St. and East River.

B. (Fig. 2): Nine out of 10 control rats were dead in 6 days. None of the animals treated with sulphanilamide died. One out of 7 rats treated with the anilide, and 2 out of 9 rats treated with the sulphone died.

Throughtout all experiments a definite increase in survival time of the fatalities among the treated animals over that of the controls was noted.

Discussion. Therapy with 4,4′-di-(acetylamino)-diphenylsulphone in infections of mice caused by pneumococci, Types VII and III was, in our experiments, not as effective as that with sulphanilamide. This is in apparent contradiction to the findings of Fourneau, *et al.*[7] and of Bauer and Rosenthal.[2] However, it appears probable that strain variations may account for the differences in the results obtained. As a matter of fact, Bauer and Rosenthal[2] encountered variation in the effectiveness of their drugs upon different types of pneumococci which they also attributed to strain differences.

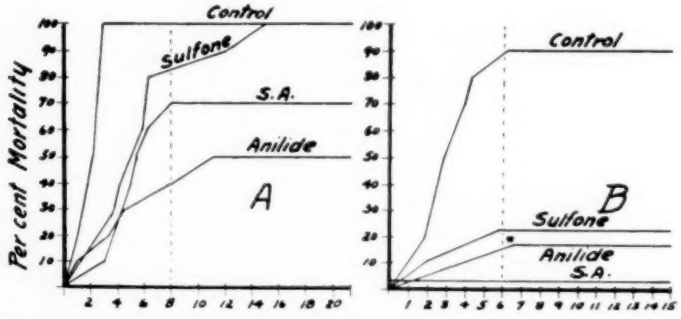

FIG. 2.—MORTALITY CURVES OF MICE AND RATS INFECTED WITH TYPE III PNEUMOCOCCUS (ALBANY).

Animals infected with diluted 18-hour broth cultures and treated orally each day. Treatment was begun 4½ hours after infection and was terminated as indicated by the vertical broken line.

A. Infection: 0.5 cc. of a 10^{-6} dilution in broth, subcutaneously (more than 100 fatal doses). *Treatment:* Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 25 mg. *B. Infection:* 0.13 cc. of a mucin suspension of an 18-hour broth culture, diluted 10^{-2}, intratracheally. *Treatment:* Controls: 10 rats, no treatment. Sulphanilamide: 10 rats, 125 mg. Sulphone: 9 rats, 125 mg. Anilide: 8 rats, 125 mg.

In experimental pneumococcal pneumonia of rats, the sulphone therapy, while not as good as that of sulphanilamide, was nevertheless of considerable value. A consideration of the relative lack of toxicity[2,5] of this drug, together with the previous favorable reports[2,7] and the above rat experiment would make it appear that this compound is worthy of clinical trial, were it not for the fact that the results in our mouse experiments were distinctly less favorable than those reported with other pneumococcal strains.[2,7] Our more recent and as yet unpublished results of sulphone therapy in Type II pneumococcal meningitis of rats were distinctly inferior to those obtained with sulphanilamide.

It has been our observation that intraperitoneal pneumococcal infections of mice constitute an extremely severe test of chemo-

therapeutic efficacy of a drug, that subcutaneous pneumococcal infections of mice give the drugs a better opportunity to manifest any possible chemotherapeutic activity,[6] and that experimental pneumococcal pneumonia of rats is probably the best method[4a,b, 8a,b] to date by which to measure antipneumococcal chemotherapeutic action.

Our search for cultures of high rat virulence has revealed a number of pneumococcal strains which, although lethal to mice in culture dilutions of 10^{-8}, are almost completely avirulent for rats. The "Enricas" Type VII strain reported above is a good illustration of this phenomenon.

Therapeutic results with 4,4′-diaminobenzenesulphonanilide were at times better than those obtained with sulphanilamide; however, its toxicity[5] would seem to preclude any extensive clinical use.

Summary. 1. 4,4′-di-(acetylamino)-diphenylsulphone has been found less effective than sulphanilamide against pneumococcal infections in mice caused by a Type VII strain and a Type III strain, as well as in pneumococcal pneumonia in rats caused by this Type III strain.

2. The results reported, although at variance with those of other investigators, probably find explanation in differences of strain susceptibility to chemotherapy.

3. 4,4′-diaminobenzenesulphonanilide, although at times more effective than sulphanilamide against the particular pneumococcus strains tested, appears too toxic to warrant clinical trial.

4. To the infections caused by Types I, II, III, and XIV pneumococci which have previously been found susceptible to therapy by certain sulphonamide and sulphone compounds may be added those caused by the Type VII pneumococcus.

5. These experiments verify previous chemotherapeutic results in penumococcal infections, namely, that little or no protection in mice may be demonstrated against more than 100 fatal doses, whereas good protection has been repeatedly reported against 10 fatal doses.

REFERENCES.

(1.) **Basman, J.**, and **Perley, A. M.**: J. Pediat., **11**, 212, 1937. (2.) **Bauer, H.**, and **Rosenthal, S. M.**: Pub. Health Rep., **53**, 40, 1938. (3.) **Branham, S. E.**, and **Rosenthal, S. M.**: Ibid., **52**, 685, 1937. (4.) **Cooper, F. B.**, and **Gross, P.**: (*a*) Proc. Soc. Exp. Biol. and Med., **36**, 678, 1937; (*b*) Ibid., p. 774. (5.) **Cooper, F. B., Gross, P.**, and **Lewis, M.**: Ibid., **38**, 375, 1938. (6.) **Cooper, F. B., Gross, P.**, and **Mellon, R. R.**: Ibid., **36**, 148, 1937. (7.) **Fourneau, E., Tréfouël, J., Tréfouël, J. Mme., Nitti, F.**, and **Bovet, D.**: Compt. rend. Acad. d. Sci., **205**, 299, 1937. (8.) **Gross, P.**, and **Cooper, F. B.**: Proc. Soc. Exp. Biol. and Med., **36**, 225, 535, 1937. (9.) **Heintzelman, J. H. L., Hadley, P. B.**, and **Mellon, R. R.**: Am. J. Med. Sci., **193**, 759, 1937. (10.) **Kreidler, W. A.**: Proc. Soc. Exp. Biol. and Med., **37**, 146, 1937. (11.) **Locke, A., Locke, R. B., Bragdon, R. J.**, and **Mellon, R. R.**: Science, **86**, 228, 1937. (12.) **Neal, J. B.**, and **Appelbaum, E.**: Am. J. Med. Sci., **195**, 175, 1937. (13.) **Rosenthal, S. M.**: (*a*) Pub. Health Rep., **52**, 48, 1937; (*b*) Ibid., p. 192. (14.) **Rosenthal, S. M., Bauer, H.**, and **Branham, S. E.**: Ibid., p. 662. (15.) **Schmidt, L. H.**: Proc. Soc. Exp. Biol. and Med., **37**, 205, 1937. (16.) **Whitby, L. E. H.**: Lancet, **1**, 1517, 1937.

STUDIES ON LIVER FUNCTION IN PNEUMOCOCCUS PNEUMONIA.*

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The investigation herein reported attempts to determine the functional changes that occur in the liver during the course of pneumococcus lobar pneumonia. The recent literature on liver function has dealt in the main either with those disease processes of the liver and bile passages which are amenable to surgical treatment, or with chronic progressive changes attended by permanent damage. There have been some efforts made to determine the functional disturbances in acute infections; these, however, have in general embodied the use of single tests.[5,7,14,18] The dangers of measuring liver function based on the ability of the organ to perform only one of its many functions, are well known. It therefore occurred to us that more accurate information might be obtained if an attempt was made to measure simultaneously more than one of the metabolic functions of the organ during the course of an acute infection. Accordingly, a series of patients suffering from lobar pneumonia were chosen for a study in which several tests were done concurrently in individual patients at varying stages of their illness. It was hoped in this way to accumulate sufficient data which, when analyzed in the light of the subsequent outcome of these cases, might provide us with further knowledge of the behavior of the liver in the course of this disease.

Material and Methods. The determinations from which an analysis was made resulted from a study of 80 cases of pneumococcus lobar pneumonia on the wards of the Fourth Medical Division of Bellevue Hospital during the season 1933–1934.† This group of cases offered an excellent opportunity for a study of this kind, in that the data on liver function was accumulated in the course of a controlled experiment to determine the therapeutic value of certain pneumococcus antisera.[4] All the patients were under the immediate control of one of us, so that methods of therapy and

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† On the services of Dr. Charles Nammack, the late Dr. Harlow Brooks, Dr. Anna von Sholly and Dr. Harry Solomon, to whom we wish to express our great indebtedness.

dietary factors were identical in the group. All the observed cases showed evidence of definite lung consolidation, and the type of infecting pneumococcus was established in every instance.

At the outset, an attempt was made to choose methods of estimating liver function that were accurate, clinically convenient and that did not involve extensive technical procedures. With this in mind, three simple test methods were used; namely, the icterus index, the urobilinogen determination of the urine, and the levulose tolerance test; the first two being a measure of the pigment excretion, and the last one of the carbohydrate metabolism of the organ.

1. *Icterus Index.* Bernheim's[1] modification of the Meulengracht test was used. This appeared to us to be a good one to use, as it is generally agreed that the icterus index is as good a guide to bilirubinemia as the quantitative van den Bergh, provided that carotinemia can be excluded. It also has the advantage of being more convenient.

The samples of blood were taken for the most part at approximately the same time of day (9 to 11 A.M.). Following coagulation of the blood, the sera were promptly separated and read in a colorimeter. A glass standard was used and readings were made, using a standard source of artificial light. Sera that showed even slight hemolysis or turbidity were discarded. These observations were made from day to day during the course of the disease. In the analysis of the results, graphs were plotted showing the daily variation of the icterus index of the serum in each case. Values up to and including 7 were regarded as normal, a figure admittedly higher than that used by most workers. Values over 7 and up to 17 were regarded as indicating latent jaundice, while values over 17 were regarded as indicating clinical icterus. In determining the trend of the icterus index in the course of the disease (*e. g.*, whether the values were stationary, rising or falling) only variations of more than 4 units between successive determinations were thought worthy of graphic analysis.

2. *Urobilinogen.* The method used was that of Wallace and Diamond,[16] a quantitative test based on the Ehrlich's aldehyde reaction. The dilutions of *freshly voided urine* ranged as follows: undiluted; 1:10; 1:20; 1:40; 1:80; 1:160; 1:320; and 1:640. Readings were made after 15 minutes so as to allow the full development of the color in the highest dilution. The urine samples were obtained from patients at the same time of day as the blood samples for icterus index (9 to 11 A.M.).

This test is thought to be extremely delicate in detecting early or slight disturbance in liver function. With impaired function, the liver cells fail to a greater or lesser extent in carrying out their task of removing urobilinogen from the blood and it is excreted in greater than usual amounts in the urine. Normally, the test should be negative with dilutions of urine greater than 1:20. Posi-

tive reaction with dilutions of 1:40 or more, were considered pathologic for the purpose of analysis.

3. *Levulose Tolerance.* Kimball is inclined to view levulose tolerance as a sensitive index of liver damage. In support of this latter claim may be cited the work of Folin and Berglund,[6] Bodansky,[2] and Cathcart and Markowitz.[3] Their results show that the metabolism of this sugar is handled almost entirely by the liver, where it is removed from the portal blood and converted into glycogen. During this process, no marked rise in the blood sugar occurs, as is seen when sugars like glucose and galactose are utilized by normal subjects. The work of Bodansky[2] clearly illustrates the difference in the metabolism of this sugar between normal animals and those in which liver damage is caused by such poisons as chloroform and phosphorus. He found after poisoning, a marked decrease in the levulose tolerance, which was comparable to the degree of liver damage noted at necropsy. From this, he concluded that this test gave reliable information in respect to the functional capacity of the liver in dogs.

In this present study, blood sugar curves were used as indices of levulose tolerance rather than determinations of urinary sugar excretion, because of the well-known fact that certain decomposition products of the sugar are of themselves non-fermentable reducing substances. Furthermore, blood sugar determinations obviate the introduction of the renal factor of permeability.

Kimball's[9] modification of the levulose tolerance test was used: 50 gm. of the sugar is administered by mouth, and the fasting, 1-hour, and 2-hour blood sugar levels are determined. The chief criterion of impaired liver function is an elevation of 30 mg. % or more above fasting level in the first hour or of 15 mg. % or more above fasting level the second hour. The levels of blood sugar which continue elevated in the second hour are important, signifying as they do, the continuing inability of the liver to metabolize the sugar. A curve that rises in the second hour greater than the level of the first hour means serious hepatic insufficiency, provided that the first rise is sufficient to prove that absorption is satisfactory.

Experimental Data. 1. *Urobilinogen Test.* Five hundred and sixty tests were done on 80 patients, the number of tests varying in the individual case from 1 to 15. An analysis of these results based on the changes noted in relation to the progress of the disease and to the final outcome, was made.

Of these 80 cases studied, 50 recovered from their disease. From Table 1, it is seen that 32 cases (64%) showed abnormal urobilinogen values at some time or other of their disease. A further attempt was made to estimate graphically the individual trend of urobilinogen excretion in recovered cases which showed abnormal levels. It is found that 27 (85%) of these 32 cases shows a falling trend in the excretion of the pigment as the disease progressed from day to day.

Of the 30 fatal cases, abnormal values were obtained in 22 (73%). Furthermore, of this group there were 5 cases (16%) showing an excretion ranging from 1:160 to 1:640, a percentage twice as high as that seen in the recovered case.

TABLE 1.—LEVELS AND TREND OF UROBILINOGEN EXCRETION IN URINE.

	Moderately high pigment excretion 1:40 to 1:80.	Markedly high pigment excretion 1:160 to 1:640.	Cases showing falling trend in pigment excretion.
Recovered cases	28 (56%)	4 (8%)	27 (85%)
Fatal cases	17 (57%)	5 (16%)	7 (32%)

An analysis of the trend of the individual curve in this fatal group shows that only 7 of 22 cases (32%) show a falling trend in urobilinogen excretion. This is a striking difference when compared with the 85% of the recovered cases which show such a trend.

It is reasonable, therefore, to infer that, while single urobilinogen determinations have little prognostic significance, serial observations in the course of the disease show falling values in the recovered cases, with rising or persistently high values in the fatal cases.

2. *Icterus Index.* Four hundred and sixty-five observations on the icterus index were made in 78 cases, the number of tests varying in the individual case from 1 to 14.

Icterus indices were obtained in 49 of the 50 recovered cases. As shown in Table 2, 35 cases (71%) had values in the range of latent jaundice, the remaining 10 (21%) exhibiting clinical jaundice. There were sufficient serial observations in 40 of the 45 recovered cases to permit an analysis of the individual trend during the course of the disease. It was found that 34 of the 40 cases (86%) showed a falling trend in the icterus index as the disease progressed.

Observations on the icterus index were made in 29 fatal cases, 22 of these (76%) showing abnormal values. Of this fatal group, 16 cases (55%) showed values within the zone of latent jaundice, the remaining 6 (21%) exhibiting clinical jaundice. It was possible to analyze the trend in 18 of these 22 cases. Only 6 of these 18 (33%) (Table 2) showed a falling trend in the icterus index as the disease progressed. If a comparison between the fatal and recovered cases is made on the basis of a falling icterus index, it is seen that 33% of the former show this trend as compared to 86% of the latter.

TABLE 2.—DEGREES OF JAUNDICE AND TREND OF ICTERUS INDEX.

	Zone of latent jaundice readings 7 to 17.	Zone of clinical jaundice readings over 17.	Per cent of cases in which icterus index tends to fall in the course of the disease.
Recovered cases	35 (71%)	10 (21%)	34 (86%)
Fatal cases	16 (55%)	6 (21%)	6 (33%)

3. *Levulose Tolerance Test.* One hundred and sixty-four tests were done on 67 patients, the number of tests varying in the individual case from 1 to 5. In 46 cases, it was further possible to follow,

by means of serial determinations, the progressive changes in liver function. The analysis here has also been on the bases of recovered and fatal cases. The results are summarized in Table 3.

TABLE 3.—NATURE AND TREND OF LEVULOSE TOLERANCE.

	Abnormal response.	Cases showing improving tolerance.
Recovered cases	33 (77%)	25 (81%)
Fatal cases	24 (100%)	2 (29%)

In all, 43 recovered cases were studied. And in 33 of these (77%) the tolerance test showed abnormal values at one time or another in the course of the disease.

Moreover, it was possible to obtain serial observations in 31 of these 33 abnormal cases. An analysis of the trends shows that in 25 of these 31 cases (81%) the levulose tolerance tends to return to normal limits during the period of observation (3 weeks). It is significant to note that none of the recovered cases showed decreasing levulose tolerance in the progress of their disease. In other words, there was never any tendency for decreasing levulose tolerance in the face of clinical improvement.

There were 24 fatal cases studied, in only 7 of which was it possible to follow by serial observations the trend of levulose tolerance. The reason for the small number of fatal cases studied serially was due to the fact that many of these cases died before this could be accomplished, some indeed being moribund on admission. In all 24 cases (100%), at least one levulose tolerance test was abnormal.

In the 7 cases where it was possible to obtain serial observations, in only 2 (29%) did the levulose tolerance tend to improve, in contrast to 81% for the recovered cases.

Variations in the Functional Tests During the Course of the Disease. It seemed of definite interest to determine the variations in the different functional tests as the disease progressed. If the daily average readings of the urobilinogen excretion in all of the recovered and fatal cases are obtained, and the results expressed in the form of a graph, certain essential facts are illustrated. Thus, from Fig. 1 there appears to be little difference in the urobilinogen excretion in the first week of the disease between the fatal and recovered cases. In the second week, there appears to be a somewhat greater divergence between the values of the two groups. This is particularly striking when the results of the third week are studied. It must be borne in mind, however, that the number of cases in this latter group are small, so that it is possible that the real difference is not as marked as the graph indicates.

Similarly, if a graph for the average daily icterus index is compiled (Fig. 2), it is seen that in the recovered cases, there is a regular descent in the curve which appears most steep in the first week. There appears also to be a plateau developing from the tenth to the

fifteenth day. In the third week, the values are, with one exception within normal limits. On the other hand, when one considers the

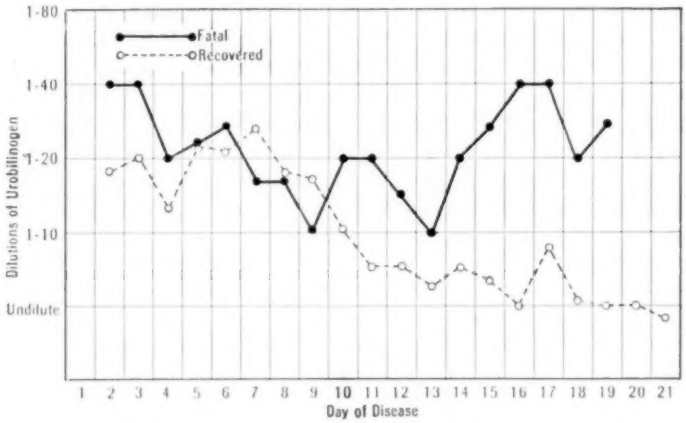

FIG. 1.—Composite daily values for urobilinogen excretion in the urine during first 3 weeks in recovered and fatal cases.

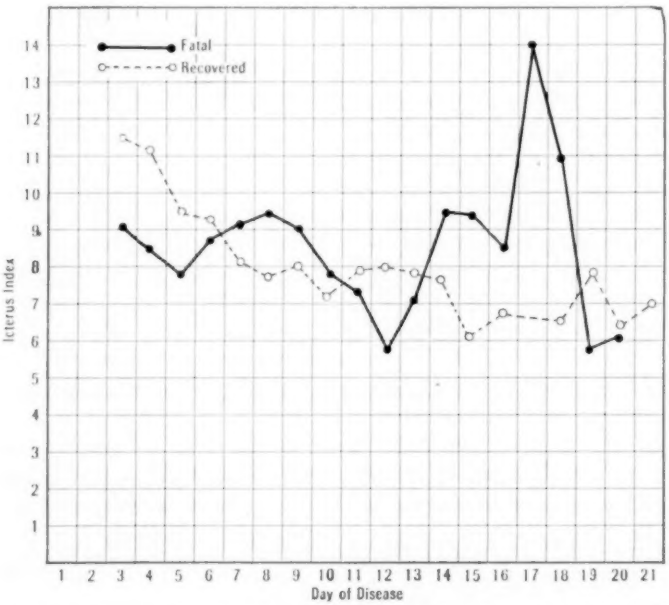

FIG. 2.—Composite values for icterus index in first 3 weeks in recovered and fatal cases.

fatal cases, one is first struck by the total irregularity of the contour of the graph. This is in some measure due to the smaller number of

observations in this group of cases. A closer analysis, however, shows that there is a tendency for the higher values to persist in the period from the sixth to the ninth day. It seems worth drawing attention to this because of the fact that the ultimate course of the disease appears to be influenced by the changes that occur in the patient in this period. That this observation in the fatal cases might be a reliable one is borne out by the fact that in this same period in the recovered cases, the average daily readings showed a constant fall. In the third week, it seems that most of the values are elevated, in contrast to the values observed in the recovered cases. If this be true, then daily observation of the icterus index in this disease might have definite prognostic importance.

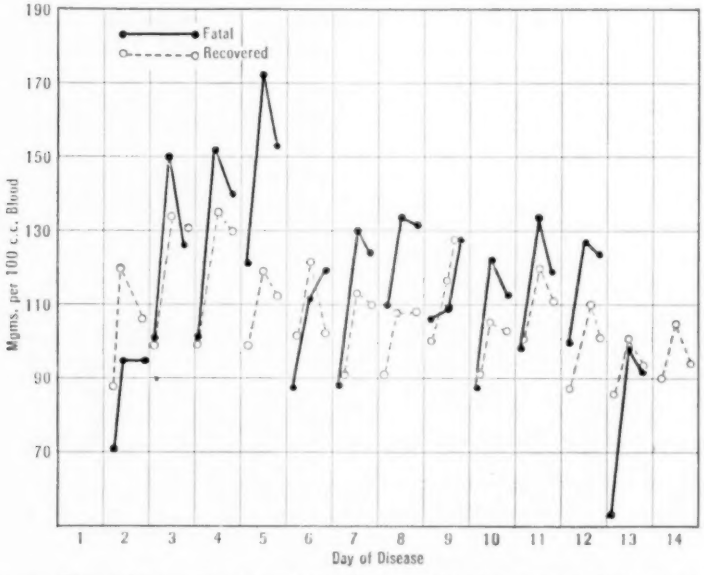

FIG. 3.—Composite curves of levulose tolerance, showing average fasting, 1-hour and 2-hour blood-sugar levels in first 2 weeks in recovered and fatal cases.

Similarly, if we analyze the levulose tolerance of these patients based on actual numerical values of their blood sugar levels, it becomes possible to compile therefrom a composite graph (Fig. 3). This illustrates a daily composite curve of the fasting, 1-hour and 2-hour blood sugar levels in both the fatal and recovered cases, during the first 2 weeks.

From this, it is seen that in the fatal cases, in almost every instance there is a well marked rise in the first hour readings above the fasting level, to be followed in most instances by either a slight fall, or even a continued rise. What is most noteworthy, however, is that the second hour level never falls within limits close to that of the fasting

level. On the other hand, analysis of the composite daily curves of the recovered cases shows levels in the first hour that are invariably lower than those seen in the fatal cases, with readings in the second hour which are not so far removed from the fasting level.

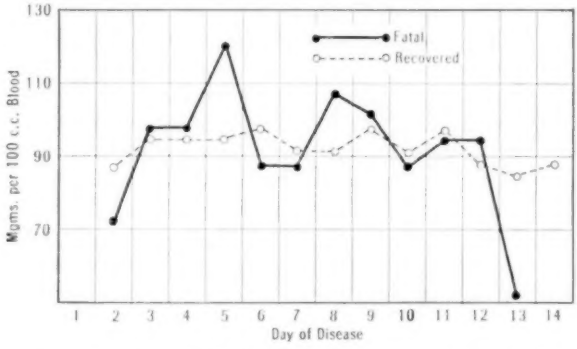

FIG. 4.—Composite fasting blood-sugar levels in recovered and fatal cases in first 2 weeks.

If one further compares the daily determination of the fasting levels in these two groups of cases (Fig. 4), it becomes at once apparent that there is a relatively narrow range of variation of the daily fasting levels in the recovered group for the first 2 weeks of the disease. Indeed, the range of fluctuation over this period is not greater than the actual technical variations that one might expect in performing this test. On the other hand, one observes from the figure the wide fluctuations of the fasting levels, throughout this same period in the fatal group, the outer limits ranging from 58 to 122 mg. per 100 cc. of blood. Aside, then, from the actual value of the levulose tolerance test, it would appear that a daily measure of the fasting blood sugar level might in itself supply us with an estimate of the function of the liver in this disease, as well as providing us with possible prognostic aid.

Relation of Liver Function to Infecting Types of Pneumococci. It seemed of interest to determine whether the functional tests demonstrated different degrees of liver damage in the different infecting types. An analysis was therefore made of the number of cases of each infecting type showing abnormal functional tests at one time or another in their disease.

TABLE 4.—ABNORMAL FUNCTIONAL TESTS IN RELATION TO INFECTING TYPES OF PNEUMOCOCCCI.

	Urobilinogen.	Icterus index.	Levulose tolerance.
Type I	12 of 18 cases (67%)	13 of 16 cases (81%)	12 of 16 cases (75%)
Type II	15 of 18 cases (83%)	16 of 18 cases (89%)	16 of 17 cases (94%)
Type III	4 of 8 cases (50%)	5 of 8 cases (63%)	5 of 5 cases (100%)
Group IV	23 of 36 cases (64%)	29 of 36 cases (81%)	24 of 29 cases (83%)

From Table 4 it would appear that the Type II cases are attended by more severe liver damage than other types. This fact is in some measure borne out by the mortality rate in the series for this type, there being 17 deaths of 25 cases (68%), a rate that is considerably higher than that observed for the other types.

Discussion. For the purposes of clarity, it might be advantageous to summarize the information obtained from the individual tests as to liver dysfunction during this acute infection.

Urobilinogen. At the outset, it is necessary to note that our estimate of liver dysfunction by means of this test has been a conservative one. In this communication, the statistical results have been based on acceptance only of the values higher than 1:20 as abnormal, a dilution admittedly higher than that on which Wallace and Diamond base their conclusions when morning specimens are used. This normal value corresponds to that used by Rabinowitz.[12] Thus, on reviewing Table 1, the incidence of abnormal urobilinogen excretion is approximately equivalent in both recovered and fatal cases. Single abnormal values by themselves, therefore, would have no prognostic significance except, perhaps, in these cases in which the urobilinogen values are high. Thus, values ranging from 1:160 to 1:640 were found twice as frequently in the fatal group. However, it seems possible to obtain more prognostic help from the use of this test when serial observations are made from time to time during the disease. That a falling curve of urobilinogen values in a given case is of good prognostic omen, is evident from the fact that 85% of the recovered cases show such a trend in contrast to 32% of the fatal cases.

There seems to be scant reference in the literature as to the changes in urobilinogen excretion in pneumonia. Wilbur and Addis[17] mention that the early appearance of large amounts of urobilin in the urine indicates a grave prognosis in pneumonia. Grönberg,[7] in a small series of otherwise healthy young men with acute respiratory disease, notes an increased urobilinogen excretion during the febrile stage. Similarly, Harris'[8] observation, in respect to pneumococcus lobar pneumonia, is in rather close agreement with our results, as he observed an abnormal increase in the urobilinogen excretion in all cases at some time during the acute febrile stage. These facts, in conjunction with our own findings, show clearly that the urobilinogen excretion is increased in pneumococcus pneumonia, and that it varies in direct relation to the severity of the disease. It also shows that unusually high abnormal values are more often associated with a fatal outcome than with recovery.

Icterus Index. A relatively larger number (92%) of the recovered cases show heightened icterus indices, in comparison to the fatal cases (76%) (Table 2). On the other hand, during the acute febrile stage, 86% of the recovered cases show a falling level, as compared to 33% in the fatal group.

The observations of other workers on estimation of the bile pigment in the blood in pneumonia are conflicting. Thus Harris,[8] by means of serum bilirubin determinations, found bile-pigment levels to be unchanged in the large majority of his cases. Bernheim,[1] on the other hand, by means of the icterus index, found that all of her 39 cases of lobar pneumonia showed increased bile pigment in the blood. These apparent discrepancies may be attributed in large part to the lack of serial observations by these authors, as it was not uncommon in our series to find values that fluctuated above or below the accepted normal on different days of the disease. Despite the different results by these two workers, they nevertheless agree that increased bile pigment in the blood seems to offer a poor prognosis. This conclusion is open to question. In this connection, pertinent is Schiff's[13] finding that in 826 cases of pneumonia 21 patients showed clinical jaundice, only 8 of whom died. He concluded from this that jaundice in pneumonia is not of specially serious prognostic omen. Similarly, Szarke's[14] observations on 900 children led him to the same conclusions. In our own series of 80 cases, we were able to recognize jaundice in only 2, both of whom recovered. There were, however, 14 other cases with icterus indices in the zone of clinical jaundice, which for some reason were not clinically recognized as icteric by us. In this group of 16 cases, there were 6 deaths (37.5%), a figure which is not sufficiently higher than the usual mortality rate for pneumococcus pneumonia in this and previous seasons, to conclude that jaundice in itself is of bad prognostic omen.

Levulose Tolerance. Our results appear to have definite significance, both as to the absolute findings and as to the general indication of liver dysfunction that this test shows in common with the icterus index and urobilinogen determinations. Thus, if one considers abnormal values only, it is seen from Table 3 that 77% of the recovered cases and 100% of the fatal cases showed evidence of impaired levulose tolerance at some stage of the disease. This finding is further strengthened by noting the trend of successive tolerance tests in individual patients who recovered or died. Thus, 81% of the recovered cases showed a return to normal in the levulose tolerance, either in the febrile or convalescent stages of their disease. This is in sharp contrast to the findings in the fatal cases, in which only 29% showed any tendency to return to normal.

These findings are of definite interest, as they show clearly the behavior of the liver in respect to carbohydrate metabolism in this acute infectious disease. A review of the literature dealing with this phase of liver function has not rewarded us with information with which our results might be compared. Thus, while levulose tolerance has been studied in many diseases, such as surgical diseases of the hepato-biliary system, toxic hepatitis, cirrhosis, catarrhal jaundice, malaria and other conditions, we were unable to find any method-

ical study of the carbohydrate function of the liver in lobar pneumonia. Williams,[18] in a study of levulose tolerance in malaria, however, secured single observations in 3 cases of lobar pneumonia and reported them as being normal. Van Creveld[15] observed that in the course of scarlet fever there is little alteration in carbohydrate tolerance until the stage of convalescence is reached, which is in direct contrast to our findings in the course of pneumococcic pneumonia.

While our findings show the value of this functional test, it remains to be seen whether frequent or daily observations of the fasting blood sugar level in this disease might not in itself provide us with equally valuable prognostic information. This is suggested by Fig. 4 in which a composite graph of the fasting levels of the fatal cases show more marked daily fluctuation than that seen in the recovered cases. Whether this is true or not can only be substantiated by further detailed study.

These findings as to the carbohydrate metabolism in our group of cases would lend support to certain recently reported therapeutic attempts[10] in which good clinical results were described, following the use of large doses of dextrose intravenously in lobar pneumonia. This is supported by the work of Opie and Alford[11] in which they found that following liver damage with chloroform, rats subsisting on a carbohydrate diet survived the intoxication, while similar animals on a meat or fat diet died.

In conclusion, it seems important to emphasize the fact that individual single tests of liver function for prognostic purposes have little or no real value. Furthermore, our results show that different test methods applied to liver function during this disease are not susceptible to too close a correlation, as it is possible to obtain a normal result with one test and an abnormal value with another test on the same day of the disease. It is evident, however, that serial tests by different methods do offer observations which when taken together give us a fairly close idea as to the severity of the disease in the individual case, providing us as well with knowledge that has some prognostic significance.

Summary. 1. Multiple methods embodying the study of pigment and carbohydrate metabolism have been utilized concurrently in a study of liver function in 80 cases of pneumococcus pneumonia.

2. The urobilinogen excretion was increased in the majority of both the fatal and recovered cases, and markedly high values of excretion are twice as frequent in the fatal group. When serial observations were made from day to day in the course of this disease, the level of pigment excretion in the urine tended to fall in the recovered cases, but to remain persistently high or to rise in the fatal group.

3. The icterus index was elevated in both fatal and recovered cases in the early stages of pneumococcus pneumonia. There was

a constant tendency to falling icterus index values in the cases that recovered and a tendency to remain high in the fatal cases.

4. There is decreased levulose tolerance in a high percentage of the recovered cases and in all of the fatal cases early in the disease. Serial observations in fatal cases show a progressive decrease in the ability to metabolize the sugar; whereas in the cases that recover, there is a progressive increase in levulose tolerance.

It is a further question whether daily determinations of fasting blood sugar levels do not provide definite information of similar significance as that afforded by levulose tolerance tests.

5. These observations stress the importance of serial determinations in any functional test in the course of the study of an acute infectious disease like pneumonia.

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REFERENCES.

(1.) **Bernheim, A. R.**: J. Am. Med. Assn., **82**, 291, 1924. (2.) **Bodansky, M.**: (*a*) J. Biol. Chem., **56**, 387, 1923; (*b*) Ibid., **58**, 515, 1923. (3.) **Cathcart, E. P.**, and **Markowitz, J.**: J. Physiol., **63**, 309, 1927. (4.) **Curphey, T. J.**, and **Baruch, H. B.**: Proc. Soc. Exp. Biol. and Med., **26**, 687, 1929. (5.) **Elton, N. W.**: (*a*) J. Michigan Med. Soc., **28**, 451, 1929; (*b*) New England J. Med., **201**, 611, 1929; (*c*) J. Lab. and Clin. Med., **17**, 217, 1931. (6.) **Folin, O.**, and **Berglund, H.**: J. Biol. Chem., **51**, 213, 1932. (7.) **Grönberg, A. E.**, and **Grönberg, A. A.**: Acta med. Scandinav., **76**, 153, 1931. (8.) **Harris, B. R.**: J. Lab. and Clin. Med., **4**, 211, 1927. (9.) **Kimball, S.**: Guy's Hosp. Rep., **82**, 157, 1932. (10.) **MacLachlan, W. W. G., Kastlin, G. J.**, and **Lynch, R.**: Am. J. Med. Sci., **179**, 93, 1930. (11.) **Opie, E. L.**, and **Alford, L. B.**: J. Am. Med. Assn., **62**, 895, 1914. (12.) **Rabinowitz, I. M.**: Canad. Med. Assn. J., **25**, 255, 1931. (13.) **Schiff, L.**: Arch. Int. Med., **40**, 800, 1927. (14.) **Szarke, V.**: Monatschr. f. Kinderh., **57**, 96, 1933. (15.) **van Creveld, S.**: Am. J. Dis. Child., **44**, 265, 1932. (16.) **Wallace, G. B.**, and **Diamond, J. S.**: Arch. Int. Med., **35**, 698, 1925. (17.) **Wilbur, R. L.**, and **Addis, T.**: Ibid., **13**, 235, 1914. (18.) **Williams, R. G.**: Lancet, **2**, 1070, 1927.

NOTE ON RAPID DESENSITIZATION IN A CASE OF HYPERSENSITIVENESS TO INSULIN.

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The purpose of this brief communication is to report the treatment and control of the diabetes in a case of hypersensitiveness to insulin by a method which, though not new in principle, has not been widely used.

Case Report. A female, age 56 (Hosp. No. 2381/36), was admitted to the Montreal General Hospital on May 1, 1936, with cellulitis of the right foot, which followed an injury to a callus. The diabetes was first discovered in April, 1927, during treatment of an axillary abscess. At that time, the

disturbance of the carbohydrate metabolism was relatively mild; after incision of the abscess, the hyperglycemia and glycosuria were well controlled with small amounts of insulin and with the low-carbohydrate-high-fat diet then in use, namely 50 gm. carbohydrate, 150 gm. fat, and 50 gm. protein. The wound healed satisfactorily. There was then no urticaria nor other sign or symptom suggesting hypersensitiveness to insulin.

TABLE 1.—SHOWING METHOD OF DESENSITIZATION IN A CASE OF HYPERSENSITIVENESS TO INSULIN.

Time.	Insulin.		Reaction.	Blood sugar, %	Remarks.
	Site.	Units.			
7.30 A.M.	I.D.	0.2	Wheal 4 sq. cm.		
7.50	I.D.	0.2	Wheal 3 sq. cm.		
8.10	I.D.	0.4	Wheal 4 sq. cm. with pseudopod		
8.15				0.192	Fasting state
8.30	I.D.	0.8	Wheal 6 sq. cm. with pseudopod		Breakfast
8.50	S.C.	0.2	Very slight induration		
9.05	S.C.	0.4	No induration		
9.20	S.C.	0.8	Slight induration		
9.40	S.C.	1.6	Moderate induration		
10.00	S.C.	1.6	Very slight induration		
10.20	S.C.	3.2	Slight induration		I.D. wheals fading
10.45	S.C.	3.2	No induration		
11.20	S.C.	6.0	Slight induration		
12.00 NOON	S.C.	9.0	Very slight induration		Lunch
12.30 P.M.	S.C.	14.0	No induration		
1.10	S.C.	20.0	No induration		
2.40	S.C.	40.0	Moderate induration		Carbohydrate, 30 gm. orally.
2.45	I.D.	4.0	Wheal 4 sq. cm. with pseudopod		
4.00	S.C.	40.0	Slight induration		Carbohydrate, 30 gm. orally.
4.25				0.059	
4.30	I.D.	4.0	Wheal 3 sq. cm.		
6.15	I.D.	4.0	Wheal 3 sq. cm. with pseudopod		Dinner
6.45	I.V.	0.4	None		I.V. 5% glucose started.
7.00	I.V.	1.0	None		
7.10	I.V.	2.0	None		
7.25	I.V.	4.0	None		I.D. reaction of 6.15 P.M. subsiding.
7.40	I.V.	8.0	None		
7.55	I.V.	12.0	None		Sips of orange juice with sugar.
8.10	I.V.	16.0	None		Sips of orange juice with sugar.
8.25	I.V.	20.0	None		Sips of orange juice with sugar.
8.50	I.V.	30.0	None		Sips of orange juice with sugar.
9.00	I.D.	4.0	Slight wheal with rapid absorption		
9.25					I.V. discont. Total 1600 cc
10.00				0.040	Carbohydrate, 15 gm. orally.

I.D. = intracutaneous. S.C. = subcutaneous. I.V. = intravenous.

The course of the diabetes was uneventful until another attack of cellulitis of the foot, October 6, 1934. Again, in spite of the infection, the diabetes was controlled satisfactorily with insulin, but each injection was followed by an urticarial reaction at the site of injection. On the 11th day of treatment, the urticaria spread over the whole body, and resistance to insulin, namely, difficult control of hyperglycemia and glycosuria was noted for the first time. A history was obtained of annually recurrent attacks of hay fever for many years, but of freedom from such attacks since 1929.

Intracutaneous tests were made with 1 unit dosages (0.1 cc.) of beef, hog, sheep, and crystalline insulin. The reactions were all alike, namely, formation of a wheal and an area of erythema of approximately 4 cm. square at 30 minutes after the injection. The insulin was therefore discontinued and an attempt made to treat the diabetes by diet alone. It was then found that though the blood was persistently hyperglycemic, the wound healed completely, but at a very slow rate. She was discharged from the hospital on March 14, 1935. On May 1, 1936, she was again admitted with cellulitis of the foot and, though there was no acidosis, the diabetes was under poor

control and could not be treated satisfactorily with diet alone. The above mentioned intracutaneous test was, therefore, repeated with crystalline insulin and it was found that the patient was still allergic.

In view of the surgical condition and the poor control of the diabetes with diet alone, an attempt was made to test the value of rapid desensitization with Connaught Laboratories commercial insulin. The amount of insulin, the time and site of each injection, the reaction to each injection, the treatment in general and results of periodic blood sugar determinations are shown in the accompanying table. The total volume of each intracutaneous injection was the same, namely, 0.1 cc.

It will be noted that practically complete desensitization was accomplished within 15 hours. At the end of 24 hours the reactions to intracutaneous tests were entirely negative.

Following the above procedure, an attempt was made to control the diabetes with the high-carbohydrate-low-caloric diet, which consisted of 220 gm. carbohydrate, 40 gm. of fat and 100 gm. of protein. It was then found that the diabetes was well controlled with 20 units of insulin daily. Two weeks later the dosage was reduced to 10 units. She was discharged from the hospital and 2 months later an intracutaneous test with 3 units of insulin resulted in formation of a slight wheal which persisted for about 1 hour. That the desensitization was sufficiently complete, however, was shown by the absence of other reactions and the satisfactory control of the diabetes. In November, 1936, when she was readmitted with a gangrenous appendix, the blood sugar was only 0.14% in the fasting state; the preoperative and postoperative management were uneventful in spite of greatly increased insulin dosage. The patient has since remained under satisfactory control without a return of the hypersensitive state, on a high-carbohydrate-low-caloric diet with small doses of insulin.

Discussion. The antigen-like reaction of insulin[4] and the clinical features of insulin hypersensitiveness[1] have recently been reviewed. Different methods of treatment of the latter have been suggested. Slow desensitization with therapeutic doses is not only uncomfortable on account of the local and general reactions, but may be harmful. When the hypersensitiveness is also accompanied by resistance to the injected insulin, this method is of little value because of the necessity of immediate control of the diabetes. Rapid desensitization has been reported to a tolerance 3,[1] 5[3] and 6.2 units.[2] In 2 of these cases the results were not permanent.[1,3] The advantages of rapid desensitization with small initial doses followed by large doses have been dealt with previously with respect to other substances possessing antigen-like reactions.[5] The case reported here is an example of the applicability of this method to cases of hypersensitiveness to insulin.

The author wishes to express his gratitude to Dr. I. M. Rabinowitch for aid in the preparation of this report, to Dr. L. H. McKim, attending surgeon, for permission to report the case, and to the patient, a registered nurse, for her coöperation.

REFERENCES.

(1.) **Allen, F. A.**, and **Scherer, L. R.**: Endocrinology, **16**, 417, 1932. (2.) **Baker, T. W.**: Arch. Int. Med., **58**, 373, 1936. (3.) **Bayer, L. M.**: J. Am. Med. Assn., **102**, 23, 1934. (4.) **Lewis, J. H.**: Ibid., **108**, 1336, 1937. (5.) **Waldbott, I. L.**, and **Ascher, M. S.**: Ann. Int. Med., **10**, 1556, 1937.

SEMEN ANALYSES OF TWO HUNDRED FERTILE MEN.

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The criteria that have been set up for the evaluation of human semen specimens have for the most part been formulated upon standards derived from the study of semen of men with histories of disturbed fertility. It is our belief, however, that a semen analysis of a series of fertile humans might more logically offer a better basis for appraisal.

Accordingly, the present investigation was undertaken to collect information relative to the semen of fertile men.

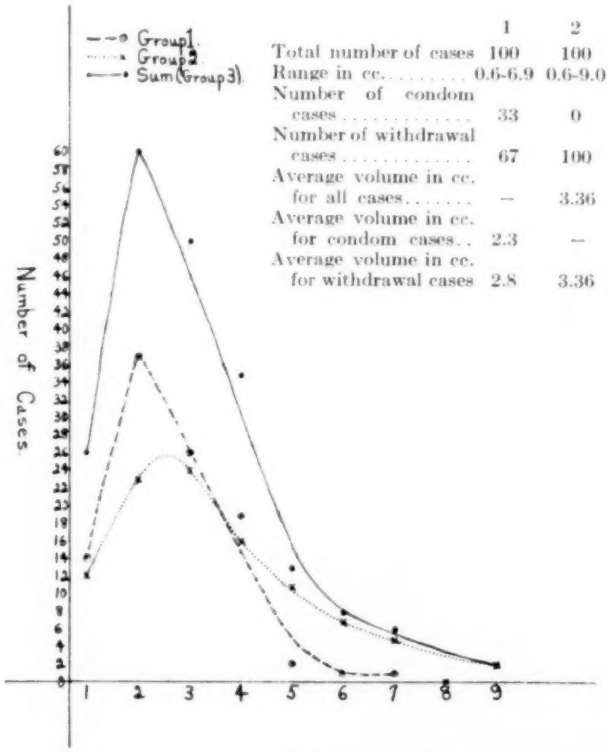
Methods. Fresh specimens were obtained from 200 husbands of pregnant women who were in the first half of gestation. All cases herein reported terminated with full-term deliveries of normal healthy children.

Two institutions served as sources for the material. The New York University College of Medicine, Department of Obstetrics and Gynecology; and the New York Hospital, Cornell University Medical College, Department of Surgery (Urology), and the Department of Obstetrics. Hereafter, the former group will be designated as Group I, and the latter as Group II.

One hundred random cases were selected and followed in each institution. The constituents of each group represented the widely varied Caucasian racial types that are to be found in metropolitan New York. Group I cases were referred from Bellevue Hospital, Department of Hospitals, New York City, which draws largely from the indigent section of the population, while Group II cases were patients of a pay clinic. Although the same plan and technique were used in each institution, each set of observations was made by independent workers, and no comparisons or analyses were attempted until both series were completed. Practical methods of semen analysis were favored above elaborate and complicated ones, and throughout the investigation a clinical viewpoint was constantly maintained. No special instruments were used which are not available in any clinical laboratory or physician's office.

Seminal specimens were collected by the patients after an advised period of 72 hours of continence. To 33 cases in Group I, washed and dried condoms were supplied, together with written instructions directing that, immediately after intercourse, the semen be emptied into a sterile test-tube, fitted with a cork stopper. The remainder (167) were instructed to collect their seminal discharge at the time of coitus by withdrawing and ejaculating directly into a large-mouthed sterilized glass test-tube. No effort was made to regulate the temperature of the specimen while in transport. More than half of the specimens were first examined within 3 hours of the time of ejaculation.

The volume of the ejaculate was measured in each case, and variations from 0.6 to 9 cc. were obtained. The average volume for all cases was 3 cc., whereas the condom group measured only an average of 2.3 cc. This in part accounts for a general lowering of the average volume of Group I patients, as compared with Group II (Fig. 1).



	1	2	3
Total number of cases	100	100	200
Range in cc.	0.6-6.9	0.6-9.0	0.6-9.0
Number of condom cases	33	0	33
Number of withdrawal cases	67	100	167
Average volume in cc. for all cases	—	3.36	3.0
Average volume in cc. for condom cases	2.3	—	2.3
Average volume in cc. for withdrawal cases	2.8	3.36	3.12

FIG. 1.—Semen volume in cubic centimeters.

The human ejaculate is a mixture of spermatozoa and the secretions from the epididymes, vasa, seminal vesicles, prostate, and the accessory glands of the urethra. The fluid content of the semen is said to carry nutritional elements for the spermatozoa. At the time of ejaculation, the specimen has a gelatinous consistency, but when it reaches the laboratory, self-liquefaction is complete and a uniform consistency is established. The spermatozoa comprise only a negligible portion of the bulk of the semen, as has been proven in vasectomized patients whose semen was repeatedly measured before operation.[5] An initial postoperative decrease in volume is completely compensated for within 3 weeks after operation.

For the study of viscosity of fluid, various elaborate instruments are available. To conform with the practical applicability of this work, simpler methods were tried. Pipettes of various kinds were standardized with distilled water, and the rate of delivery was compared with that of semen. The factor of surface tension, however, is not eliminated in this method. A set of instruments of the Ostwald type, having different sized bores, could be adapted for use with semen. As one acquires experience in handling many specimens, it becomes relatively easy to judge normal viscosity and

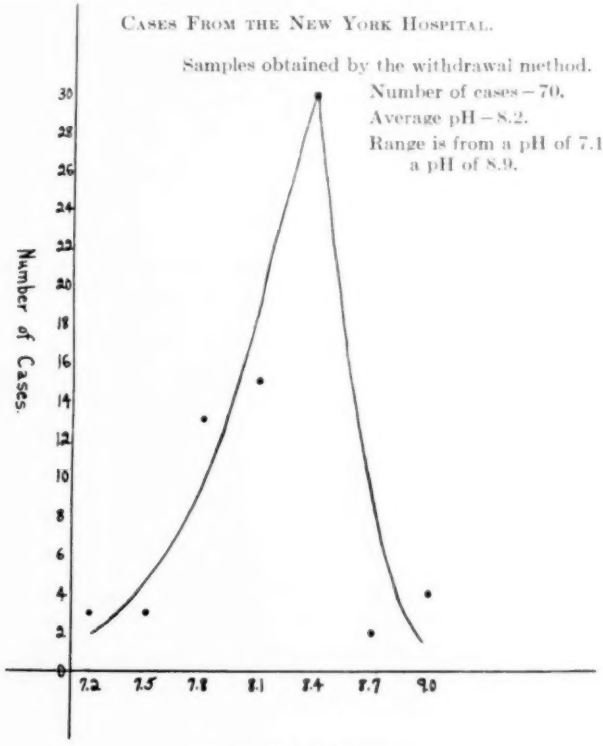


Fig. 2.—pH of the semen.

to evaluate turbidity without special instruments. Cary's[3] simple method of testing the viscosity of cervical mucus was utilized for semen.

Messer and Almquest[12] have shown that the hydrogen-ion concentration of semen should be ascertained after precautions have been taken to prevent loss of carbon dioxide, due to exposure to air. The potentiometric method, using a quinhydrone electrode upon the semen collected under a layer of oil is too complicated for practical clinical application. Hydrogen-ion determinations were

made by the Pfaff colorimeter upon 68 specimens, and disclosed a range of 7.1 to 8.9. Messer and Almquest in 27 determinations found the mean pH to be 7.2, with individual variations over a range of 0.7 to 0.8 pH units. Baker[1] states that all sperm are killed at a pH of 5, and that they also exhibit poor motility between 6 and 6.9.

As can be seen from the accompanying charts, no correlation can be drawn between the hydrogen-ion concentration, as obtained by

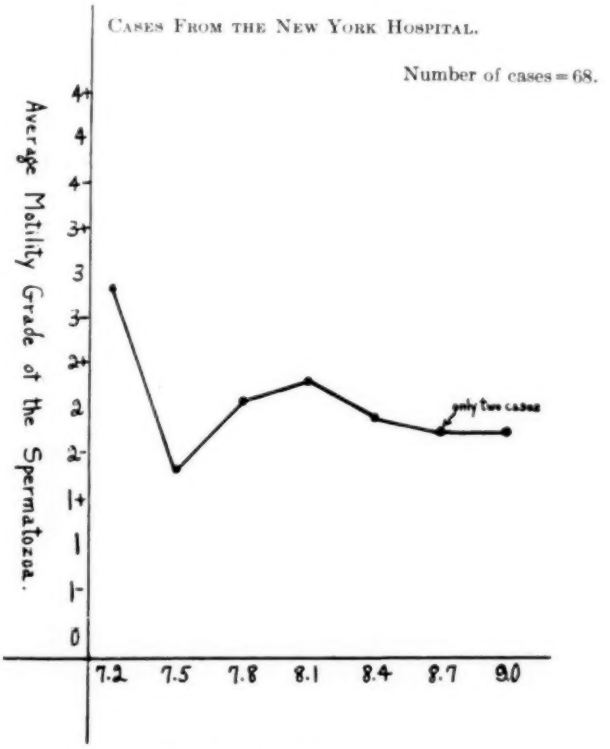


Fig. 3.—pH of the semen.

the colorimetric method, and the type and character of motility. Hence, when motility is satisfactory, it is unlikely that additional information is to be gained by a determination of the pH of seminal fluids (Figs. 2 and 3).

It is an accepted fact that living spermatozoa consume oxygen, give off carbon dioxide, and probably utilize sugar in their metabolism. Even approximate quantitative determination of sugar content of the semen requires time, special skill, and apparatus not generally possessed by the practising physician. The Benedict

modification of the Folin-Wu method for blood analysis was used to determine the sugar content of the semen.

Estimations were done in 64 specimens, using 0.5 cc. of semen as a sample for estimating the total reducible substance in the specimen. Ranges from 9 to 810 mg. per 100 cc. were obtained, the average being 306 mg. per 100 cc. of semen (Fig. 4).

A comparison between the grade of motility and the sugar content shows no clinical correlation. Accordingly, no apparent practical advantages are to be derived from this test (Fig. 5).

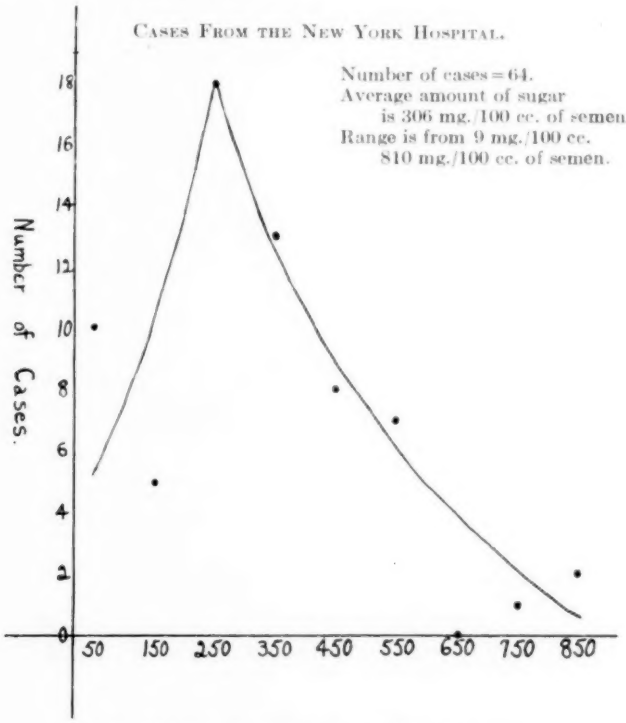


Fig. 4.—Amount of sugar in mg. per 100 cc. of semen.

The motility of the specimen should be evaluated on the basis of various factors; *i. e.*, type and aggressiveness of activity, percentage of inactive cells, and duration of motility. If the motility is poor, more than one specimen should be examined.

The method of collection is important in preserving good motility. A so-called semen sample produced by prostatic massage is mentioned only to be condemned, for it contains no more than the prostatic secretions with sometimes a few sluggish spermatozoa. Collection and delivery in rubber or skin condoms is the most com-

mon practice in clinical examinations. Because the former contains mica dust, sulphur, and benzine derivatives, and the skin condom must be wet before use, a definite damage is often done to the specimen by these contaminants. This can be demonstrated when the motility of the sperm so collected is compared with that of a withdrawal specimen from the same individual. Washed and dried condoms were supposed to have overcome this objection, but in 33 cases where these were used for collection, the motility was definitely inferior to the rest of the series.

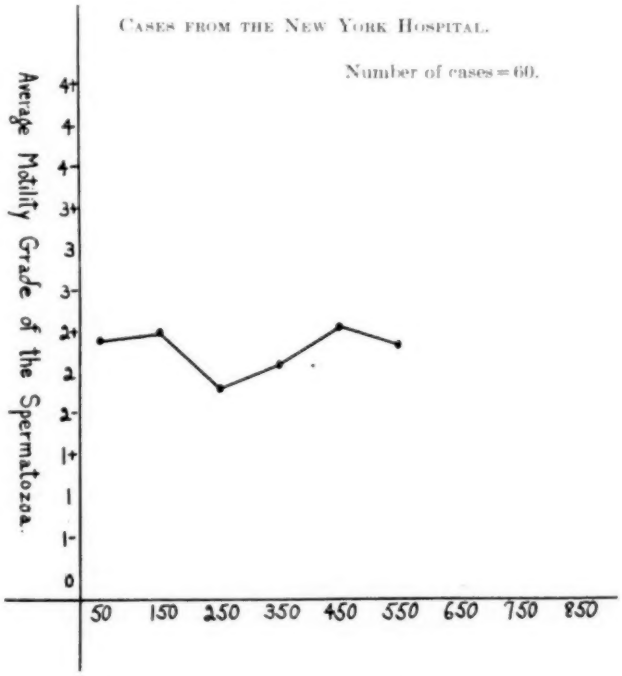


Fig. 5.—Amount of sugar in mg. per 100 cc. of semen.

Our experience bears out Belding's[2] contention that the optimal temperature for the preservation of motility is between 8 and 20° C. In good specimens, it is unusual to find appreciable change in the motility during the first 3 hours after ejaculation.

Active motility is considered to be a progressive, space-gaining movement across the microscopic field. Notations were made, using a slide and coverslip preparation, with a 4 mm. objective. In the majority of the cases, observations on the grade of motility were done within 3 hours. With few exceptions it was possible to make interval examinations every 3 hours during the day until the motility had stopped. Percentage of motility, as listed in Table A, means

the number of actively motile cells in relation to the total number of cells seen in each field.

% motility.	Grading.	% motility.	Grading.	% motility.	Grading.
0	0	35%	2	70%	3
5%	1−	40%	2	75%	3+
10%	1−	45%	2	80%	3+ or 4−
15%	1−	50%	2+	85%	4−
20%	1+ or 2−	55%	2+	90%	4
25%	2−	60%	2+ or 3−	95%	4+
30%	2−	65%	3−		

TABLE A.

At the end of 3 hours the average motility for 202 specimens was Grade 3−. During the course of these observations, Group I specimens were kept at room temperature and Group II at 20° C.

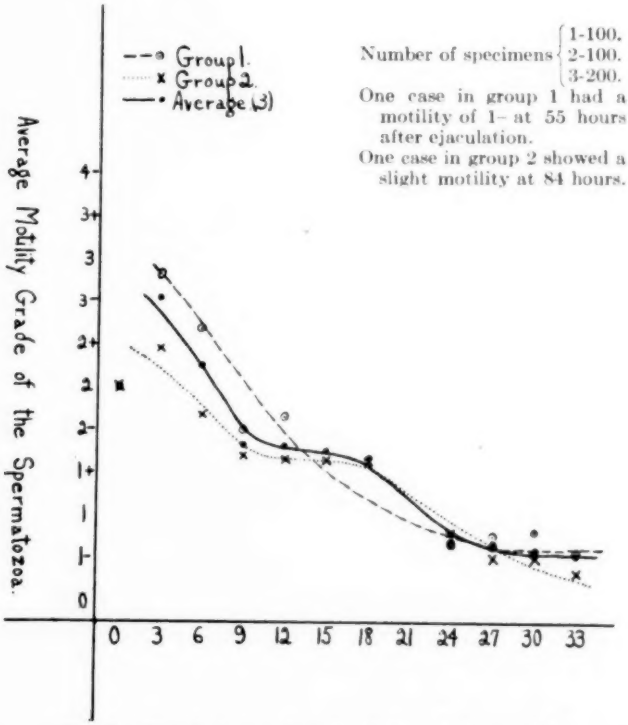


FIG. 6.—Time in hours after ejaculation of the semen.

There was no motility in 5 of 169 withdrawal specimens. One of these was first seen at the end of 30 hours. Another was collected and delivered in a perfume bottle, which may have caused contamination, thus accounting for this defect. Of the 33 condom

cases, 9 showed no initial motility. One specimen of Group I exhibited motility 55 hours after ejaculation, and in Group II, one showed slight motility at 84 hours.

Figure 6 shows the relationship of the grade of motility as compared to the age of the specimen. Prompt examinations of the semen are to be desired, but specimens presenting better grades of motility may be evaluated 3 to 9 hours after collection.

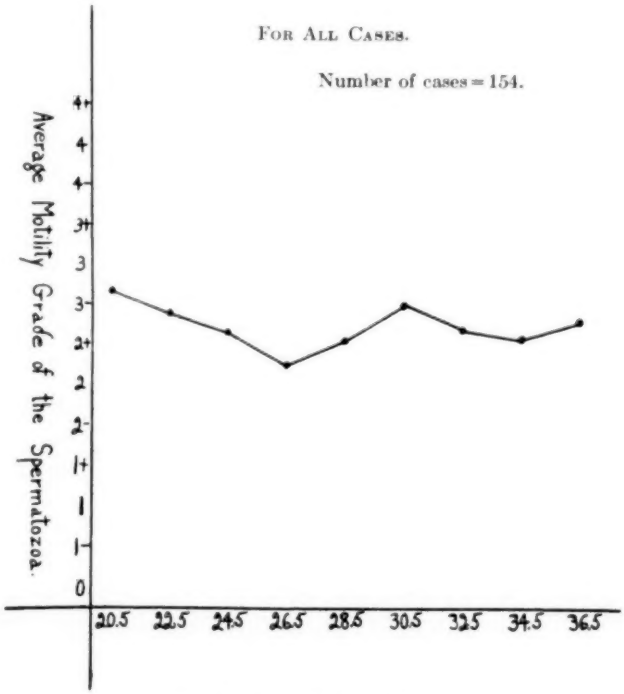
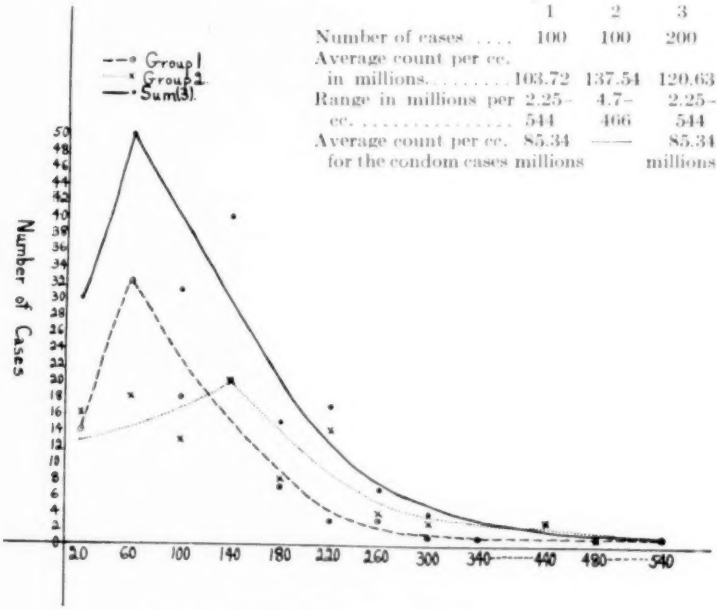


Fig. 7.—Age of men in years.

Figure 7 compares the type of motility with the age of the men. No profitable deductions can be drawn.

The number of spermatozoa found in 1 cc. is commonly used to designate the cell count. A determination of the number of sperm in the total ejaculate is obtained by multiplying the count per cc. by the volume of the entire ejaculate. The technique described by Macomber and Saunders,[10] Vose,[14] and Belding[2] was followed. More accurate counts are made within the first 3 hours after ejaculation, for after that period a certain amount of agglutination of the spermatozoa has occurred. Slight clumping of the cells occurs with ageing of the specimen, and errors are introduced which are not present in the fresh ejaculate. Each specimen was thoroughly

mixed by shaking before a sample was taken, and at least three separate counts were made. If numerous cells were present as observed through the high dry lens, a 1 to 20 dilution was used. If the number of spermatozoa was obviously reduced, a 1 to 10 dilution was preferred. All dilutions were made with standardized white blood cell pipettes, and a fluid consisting of a saturated solution of sodium bicarbonate and 1% phenol. A counting chamber with the Neubauer ruling was employed. The area studied was the red blood cell field, which occupies a space 1 by 1 sq. mm. If the cells found therein were few in number, all those within this



	1	2	3
Number of cases	100	100	200
Average count per cc. in millions	103.72	137.54	120.63
Range in millions per cc.	2.25–544	4.7–466	2.25–544
Average count per cc. for the condom cases	85.34 millions	——	85.34 millions

FIG. 8.—Spermatozoa count in millions per cc.

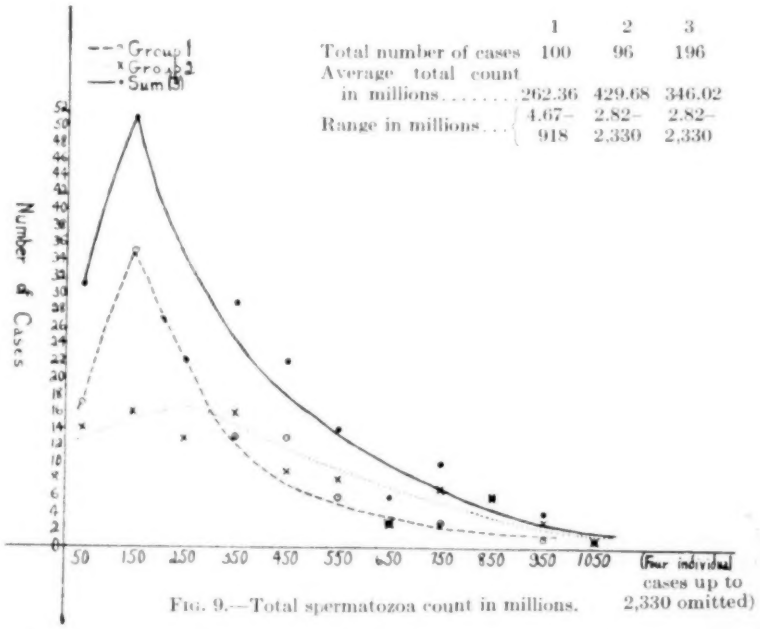
area were counted. If, however, many cells were found in the field, accurate results were obtained by counting 5 blocks of 16 squares, or one-fifth of the red blood cell field. By adding 6 ciphers to the latter figure, the number of sperm in 1 cc. was arrived at. It is recognized that a 10% variation in the final counts is not inconsistent with good technique.

Meaker[11] states in his text: "Most men who are highly fertile have counts over 100,000,000, and in our experience no pregnancy has occurred where the sperm count was below 60,000,000. Macomber and Saunders, in a series of 244 cases of fertile and sterile matings, have 4 cases where pregnancies have occurred with counts less than 60,000,000. It is assumed that both these investigators were quoting counts of sperm content per cc.

Belding[2] believes that the count per cc. may vary according to the activity of the prostate and seminal vesicles, and therefore considers the total count for the ejaculate to be more consistent and reliable.

Our results are tabulated in both cubic centimeters and total number of spermatozoa per ejaculate (Fig. 8).

The count per cc. varied from 2,250,000 to 544,000,000; the average being 120,630,000.



	1	2	3
Total number of cases	100	96	196
Average total count in millions	262.36	429.68	346.02
Range in millions	4.67–918	2.82–2,330	2.82–2,330

FIG. 9.—Total spermatozoa count in millions.

In the group of cases where condoms were used for collection, the counts were consistently lower, reaching the average of 85,340,000 per cc. This discrepancy might be partially explained by the presence of extraneous materials in the sheaths, which caused agglutination of the sperm, and prohibited uniform dilution.

In the accompanying tabulation, cases which showed a count below 60,000,000 per cc. were summarized.

(Count (per cc.).	Group I cases.	Group II cases.	Total cases.
Less than 20,000,000	9	1	10
Between 20,000,000 and 40,000,000	5	15	20
Between 40,000,000 and 60,000,000	14	8	22
	28	24	52

Thus it is seen that more than one-quarter of the cases studied had cell counts under 60,000,000 per cc. (Fig. 9).

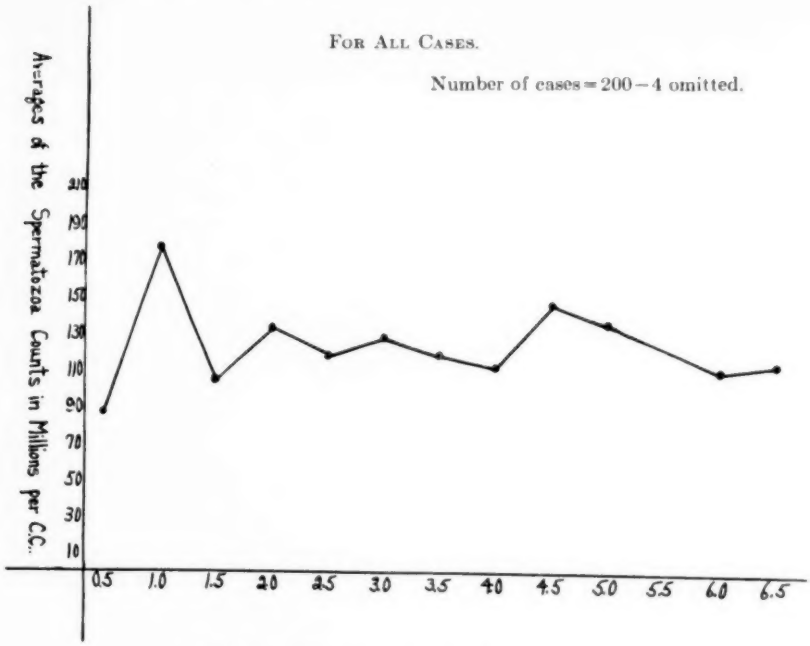


Fig. 10.—Semen volume in cubic centimeters.

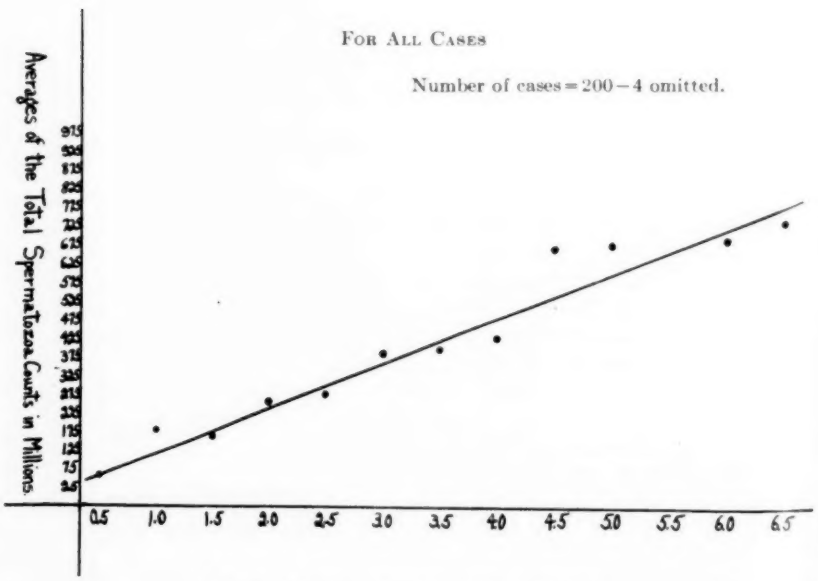


Fig. 11.—Semen volume in cubic centimeters.

The total number of spermatozoa in the ejaculates varied from 2,820,000 to as high as 2,330,000,000; the average being 346,020,000. Compiling the cases with low total counts, the following summary may be made.

Count (total).	Group I cases.	Group II cases.	Total cases.
Less than 50,000,000	6	5	11
Between 50,000,000 and 100,000,000 . . .	11	9	20
Between 100,000,000 and 150,000,000 . . .	23	8	31
	40	22	62

No relationship exists between the amount of ejaculate and the spermatozoa count per cc. (Fig. 10).

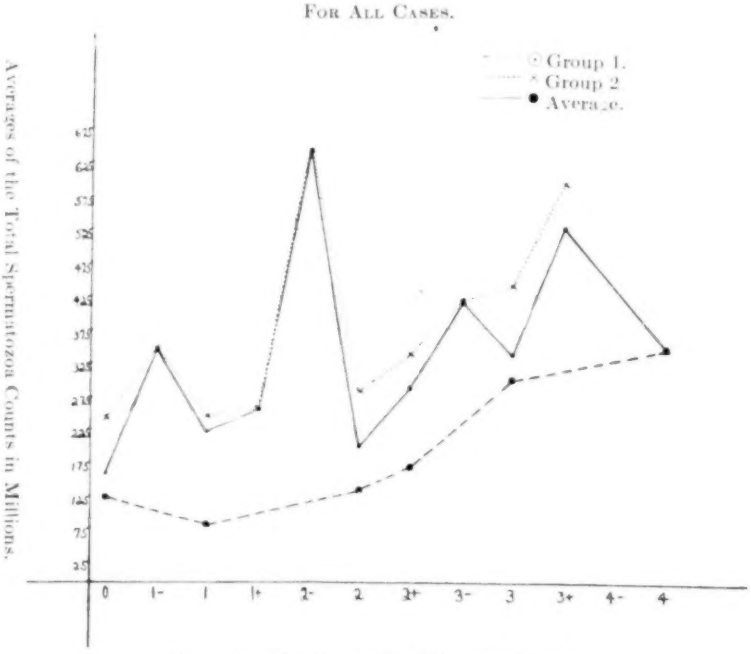


Fig. 12.—Motility grade of the spermatozoa.

Hence, it appears that a small volume does not necessarily indicate a concentration of the cellular elements, nor a large volume a higher dilution.

Figure 11 illustrates that in general the larger the volume, the higher the total cell count.

Specimens with higher cell content with few exceptions exhibit better grades of motility (Fig. 12).

Let us emphasize here that these relationships between volume and cell content, and between volume and motility, are based on a

population study and cannot be used as a standard for the individual.

Williams and Savage,[15] in 1925, investigated the semen of bulls with "good" and "bad" breeding records. Detailed measurements were taken of the head of the sperm, and conclusions were drawn that the "morphology of the head of the sperm constitutes the greatest single source of information as to the fitness of cells for reproduction." Bulls with poor breeding records were found to have an average of 50.1% abnormal cells, while in animals with good breeding records, the abnormal sperm count did not exceed

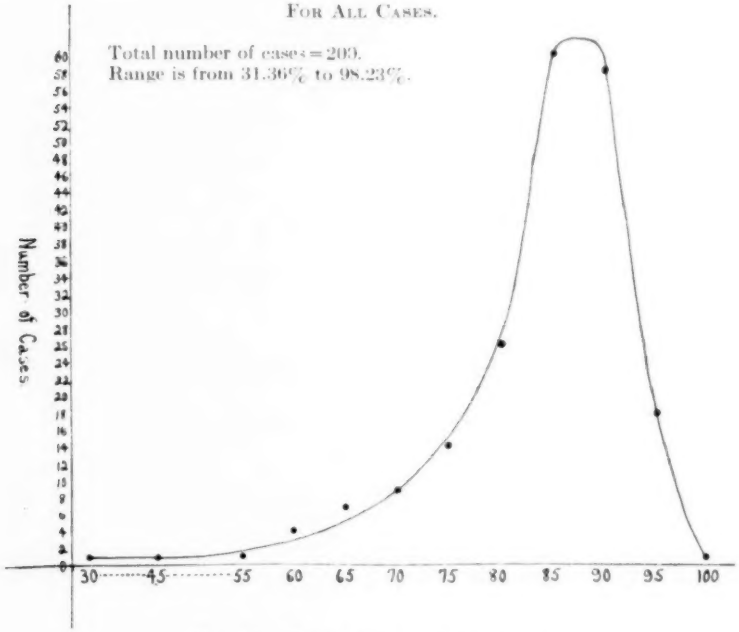


Fig. 13.—Per cent of oval spermatozoa.

16.6%. Lagerlof[7] reached similar conclusions after investigating the semen of 250 bulls. Woloskow,[16] in an investigation on stallions, found that a foaling percentage of 89 was obtained where the abnormal cells were as high as 30%. McKenzie and Phillips[9] estimated that the count of abnormal sperm in semen of boars should not exceed 10 to 15% for high fertility. McKenzie and Berliner[8] have recently found that there is a seasonal variation in the percentage of abnormal forms in Shropshire rams. Ewes that were inseminated with semen during the off-season, when abnormal forms were as high as 84.8%, failed to become pregnant. When the percentage of abnormal forms dropped below 15%, all ewes inseminated with the semen conceived.

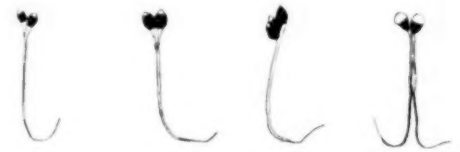
Moench[13] adapted Williams and Savage's method of classification of sperm analysis. In 1931, he reported the results of his analysis

MORPHOLOGY OF SPERMATOZOA.

Oval. Oval with vacuole. Oval with cytoplasm. Oval side view. Oval with coiled tail.

Tapering-1. Tapering-1. Tapering-2. Tapering-3. Tapering-3.

Round, large. Round, small. Giant. Giant. Pinhead.



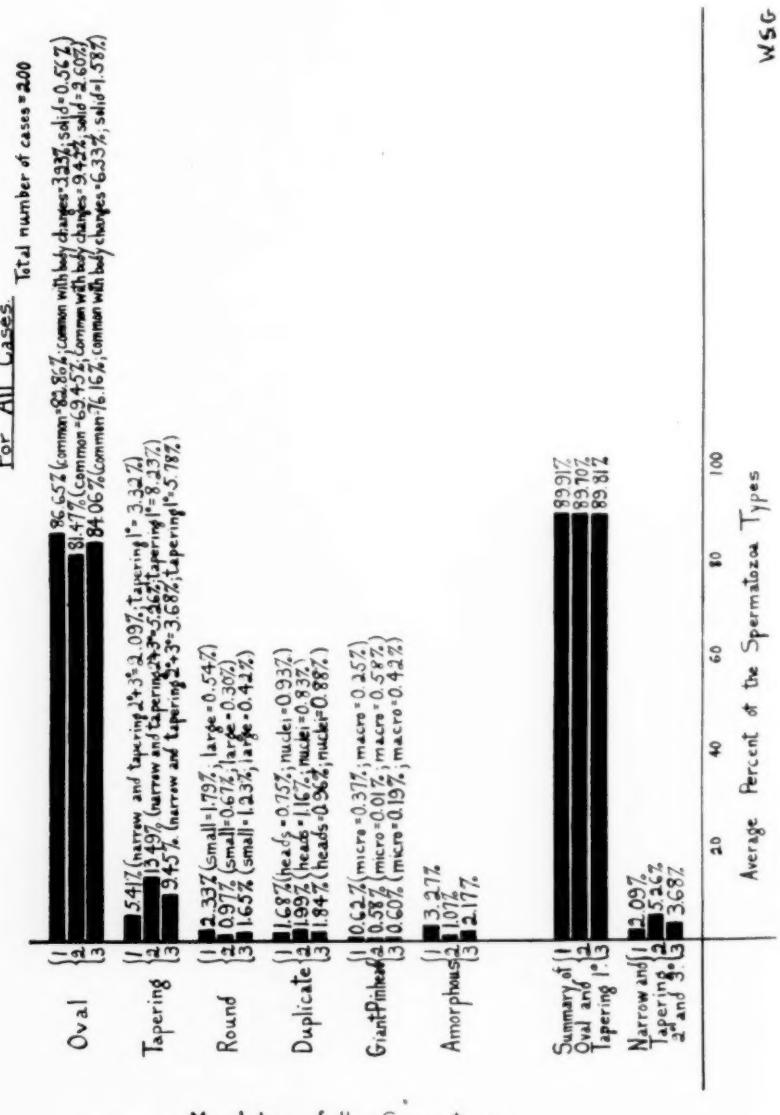
Duplicate.

Duplicate.

Amorphous.

Drawing A.

of 37 fertile normal men, and came to the conclusion that abnormal sperm heads never exceeded 19 to 20%. He assumed that fertility is impaired when abnormalities reach 20 to 22%, and that "clinical sterility" was usually present if 25% abnormal forms were found.



Bar Graph A.

Kleegman[6] reviewed the semen of 25 husbands of marriages where conception took place and normal children were born. Only in a single case was there an abnormal count as high as 25%.

On the other hand, Macomber and Saunders[10] believe that information obtained from the cell count per cc. is as important as a study of the morphology of the sperm. They state that the "enumeration of spermatozoa gives identical information as to the fertility as does head measurement."

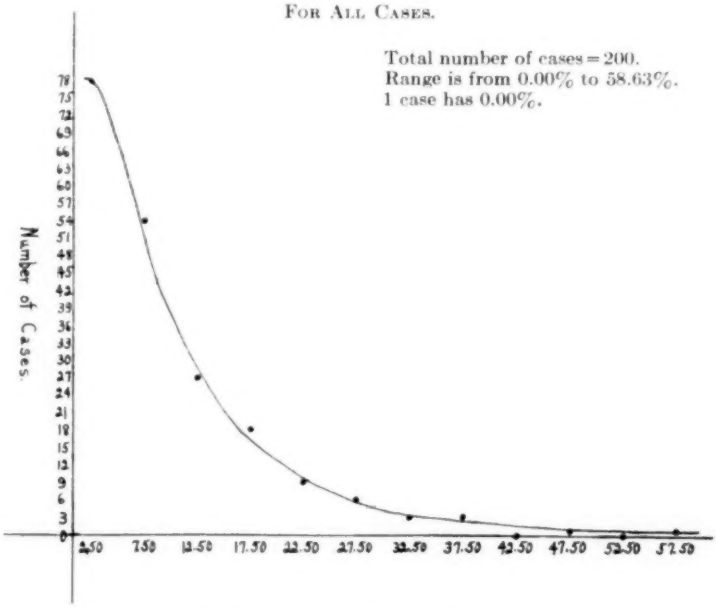


Fig. 14.—Per cent of all tapering types.

The time-consuming and complicated methods of accurately measuring the size of each sperm head did not seem practical or adaptable to clinical usage. Hence, the morphologic studies were done as follows:

A thin spread of semen was prepared on a clean glass slide. While still wet it was immersed in Schaudinn's solution to prevent distortion in drying. The preparation was then stained by eosin and hemotoxylin as described in a previous article by one of us.[4]

Three hundred or more cells were counted according to their morphologic type under oil-immersion magnification. The various types of cells were listed only as to their incidence or occurrence, and no preconceived opinions as to "normal" or "abnormal" cells were permitted. Six main types were thereafter recognized: 1, Oval; 2, Tapering; 3, Round; 4, Duplicate; 5, Giant and Pinhead; 6, Amorphous.

No word description can better the accompanying drawings to illustrate these types (Drawing A and Bar Graph A).

The various cells are quite distinctive in their shape and appearance.

The oval cells are far the most common cell type. Their average in the entire series of 200 cases was 84.06%, with a range from 31.36 to 98.23% (Fig. 13).

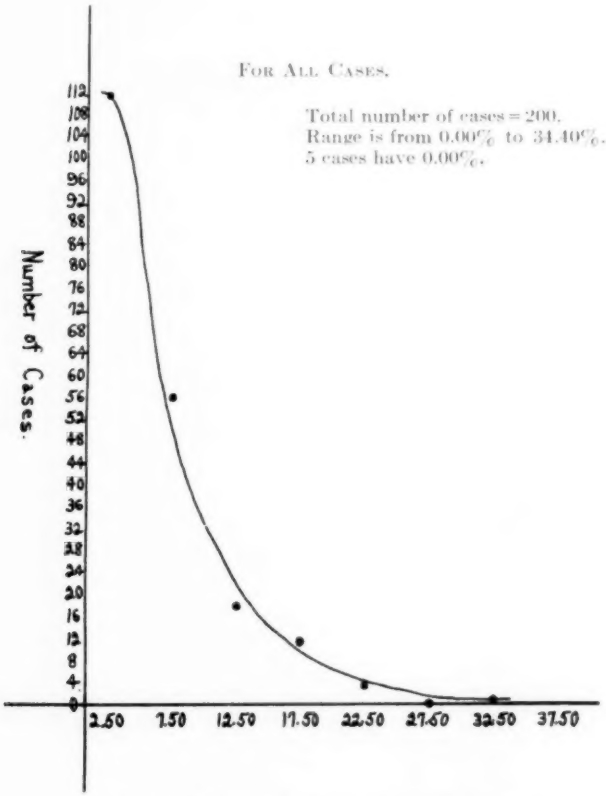


Fig. 15.—Per cent of tapering 1° spermatozoa.

Tapering cells were subdivided into 3 classes: Tapering 1, Tapering 2, and Tapering 3. There is no difficulty in differentiating the latter two types. Tapering 1, however, closely resembles the normal oval form. Grouping all tapering cells together, an average of 9.45% was obtained, with a range from 0 to 58.63% (Fig. 14).

If the Tapering 1 cells are considered alone, they are found to have an incidence of 5.78%, with a wide range of 0 to 34.4% (Fig. 15).

It is apparent that differences of opinion may exist between two or more observers, in distinguishing Tapering 1 cells from the usual oval type. (Note the discrepancy between Group I and Group II in Bar Graph A).

Because of their close resemblance, the Oval and Tapering 1 cells were classified together, and considered one and the same. A much more consistent agreement by the two laboratories was thus

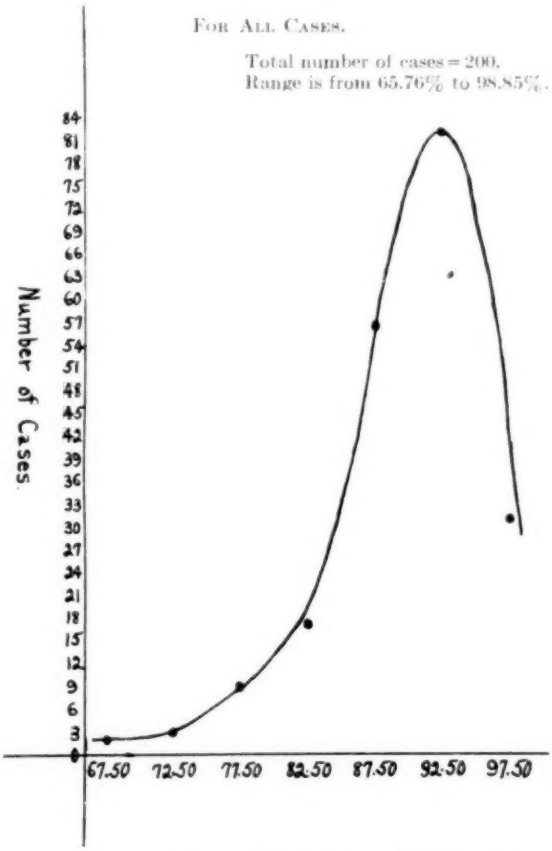


Fig. 16.—Per cent of oval and tapering 1° forms.

reached with an actual difference of only 0.2%. Under this plan, an average of 89.81% was found, with a range of 65.76 to 98.85% (Fig. 16).

If the Tapering 1 form is to be considered an abnormal cell, 3 of our cases would have 50% or more and 37 others 25% or more of atypical spermatozoa. On the other hand, if this cell is classified as normal and grouped with the Oval type, there were 5 cases with

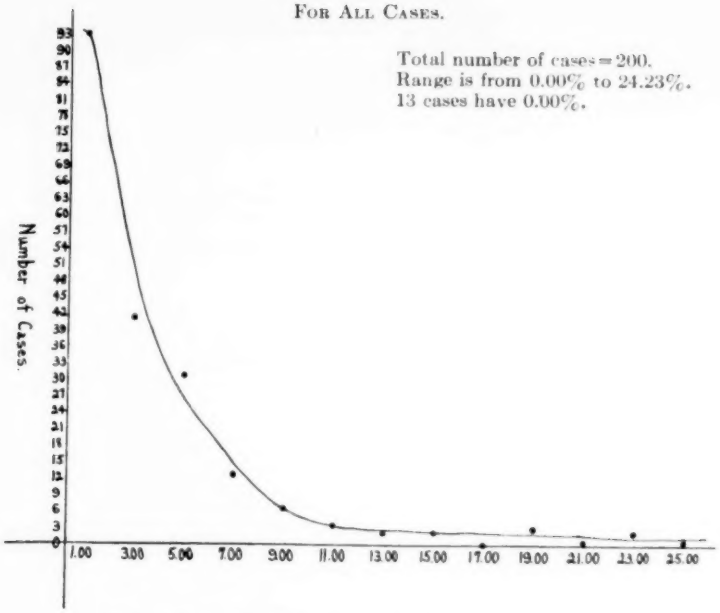


Fig. 17.—Per cent of narrow and tapering 2° + 3° types.

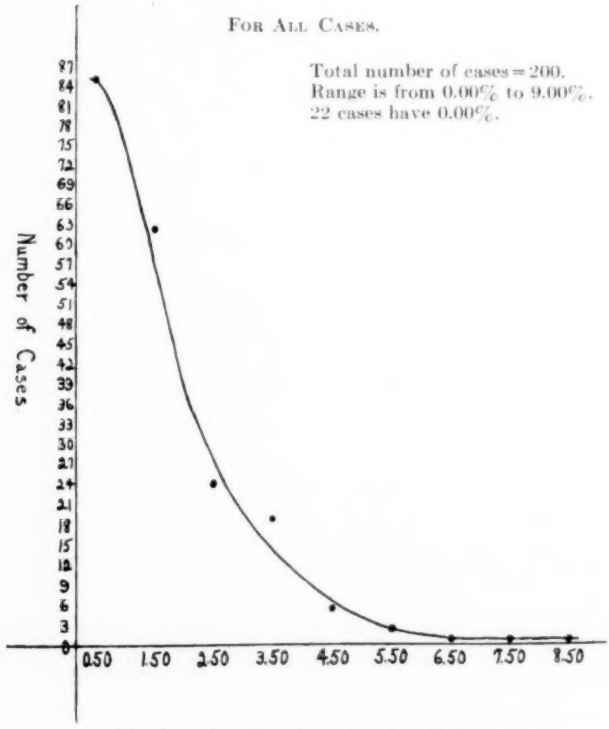


Fig. 18.—Per cent of round spermatozoa.

25% or more abnormal cells. In 1 case, 32.5% abnormal cells were found.

Unusual emphasis has been given herein to the discussion of the Tapering 1 cell because of the confusion regarding its classification. Statistically and morphologically, there seems no doubt that this rightfully should be considered an Oval spermatozoön.

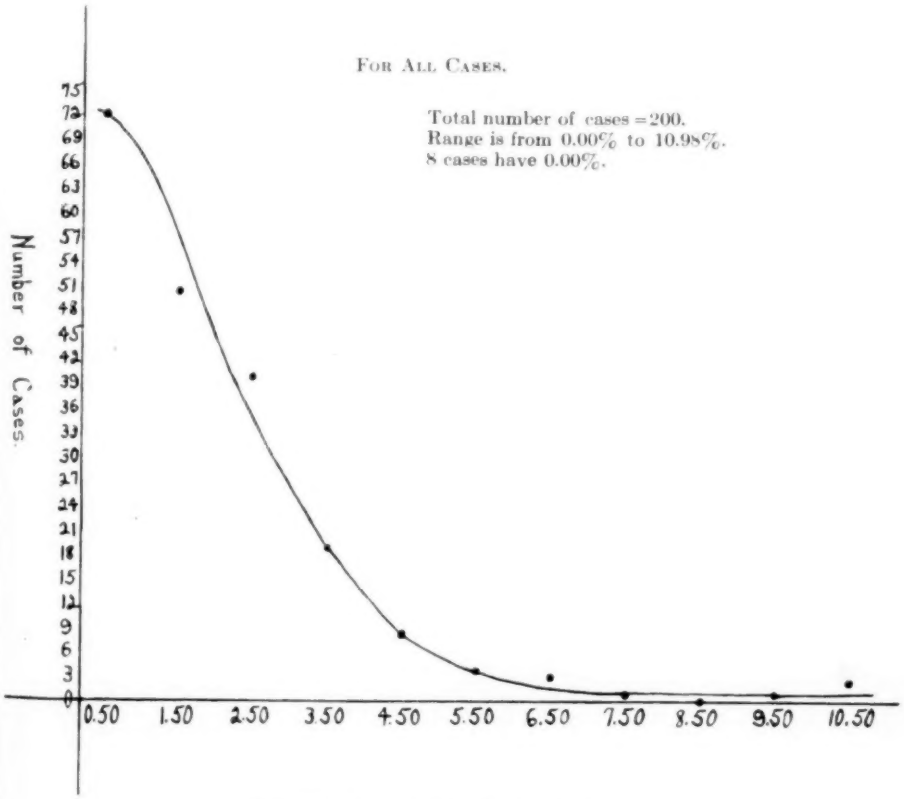


Fig. 19.—Per cent of duplicate spermatozoa.

If the Taperings 2 and 3 cells were grouped together with the narrow type (which may be side views of these), an average of 3.68% was obtained, with a range of 0 to 24.23% (Fig. 17).

The above findings are at variance with Moench's limit of 8.5% for fertile specimens. In 11% of our cases these cell types were present beyond that figure.

Round forms were comparatively rare, having an incidence of 1.65%, and a range from 0 to 9% (Fig. 18).

Duplicate cells comprised double nuclei, double heads, or double

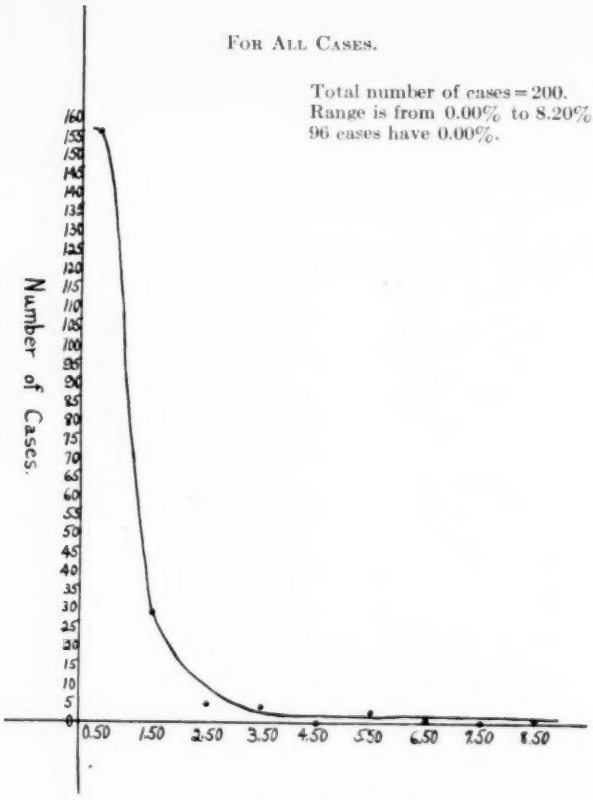


Fig. 20.—Per cent of giant and pinhead spermatozoa.

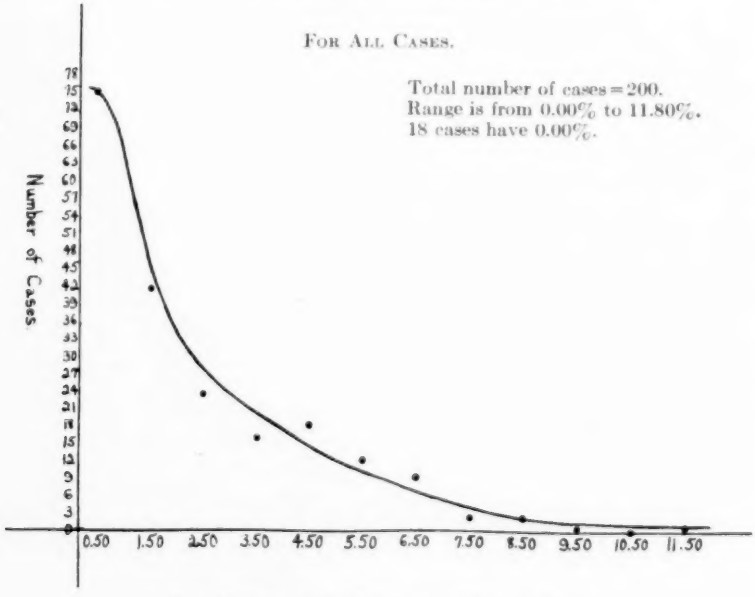


Fig. 21.—Per cent of amorphous spermatozoa.

tails. They averaged as a group 1.84%, and had a range from 0 to 10.98% (Fig. 19).

The Giant and Pinhead groups occurred most rarely, having an average of 0.6%, with a range of from 0 to 8.2% (Fig. 20).

The Amorphous group, so-called because their unusual varieties in shape defy any appropriate name, had an average of 2.1%, with a range of 0 to 11.8% (Fig. 21).

Summary and Conclusions. 1. Detailed analyses of the semen of 200 fertile men whose wives were in the first half of gestation are herein reported.

2. The volume of ejaculate averaged 3 cc. when collected by withdrawal, and 2.3 cc. by condom.

3. When motility is satisfactory a determination of the pH of semen is unnecessary.

4. Estimation of the sugar content of semen has no apparent clinical value.

5. Motility is apt to be impaired when the condom is used for collection.

6. A method of appraising motility is discussed.

7. No relationship was demonstrated between the grade of motility of the spermatozoa and the age of the men.

8. Spermatozoa counts averaged 120,530,000 per cc.

9. Twenty-five per cent of the cases had spermatozoa counts below 60,000,000 per cc.

10. No constant relationship exists between the amount of ejaculate and the spermatozoa count per cc.

11. Larger ejaculates usually have higher total cell contents.

12. Specimens with high cell counts generally exhibit better motility.

13. Differential morphologic counts were done on each specimen.

14. Oval cells, including Tapering 1, averaged 89.81%.

15. If Tapering 1 is to be considered an abnormal cell, 3 of our cases would have 50% or more, and 37, 25% or more atypical spermatozoa.

16. Since Tapering 1 cell so closely resembles the oval form, we believe they should be classed together.

17. Taperings 2 and 3 averaged 3.68%, but in 22 of the cases they were found in excess of 8.5%.

18. From previous clinical experience and investigative study, it is the opinion of the authors that an assay of fecundity includes a consideration of volume, grade of motility, number of spermatozoa and percentage of abnormal forms. The fertilizing value of semen depends on a combination of all four of these basic factors, rather than any single one alone.

The generosity of the National Research Council permitted the equipping of a laboratory and the defrayal of expenses for the portion of the investigation carried on at the New York Hospital.

Miss Frances E. Scudder, B.S., most ably conducted the laboratory analyses at the New York Hospital.

The authors wish to express their sincere appreciation for the invaluable assistance of Mr. William S. Goldfarb, M.S., B.S., for his expert summary and arrangement of the biometric statistics.

The coöperation of Miss Jessie Stewart Ross, Social Service, Bellevue Hospital is most deeply appreciated.

REFERENCES.

(1.) **Baker, J. R.**: J. Hyg., **31**, 189, 1931. (2.) **Belding, D. L.**: Am. J. Obst. and Gynec., **26**, 868, 1933; **27**, 25, 1934. (3.) **Cary, W. H.**: New York State J. Med., **30**, 131, 1930. (4.) **Cary, W. H.**, and **Hotchkiss, R. S.**: J. Am. Med. Assn., **102**, 587, 1934. (5.) **Hotchkiss, R. S.**: J. Contracept., **1**, 31, 1936. (6.) **Kleegman, S. J.**: Am. J. Surg., **33**, 392, 1936. (7.) **Lagerlof, N.**: Ztschr. f. Züchtung, B., Bd., **32**, S. 47–93, 1935. (8.) **McKenzie, F. F.**, and **Berliner, V.**: Univ. Missouri Agric. Exp. Sta., Bull. 265, 1937. (9.) **McKenzie, F. F.**, and **Phillips, R. W.**: Ibid., Bull. 328, 1933. (10.) **Macomber, D.**, and **Saunders, M. B.**: New England J. Med., **200**, 981, 1929. (11.) **Meaker, S. R.**: Human Sterility, Baltimore, The Williams & Wilkins Company, 1934. (12.) **Messer, F. C.**, and **Almquest, B. R.**: J. Urol., **37**, 319, 1937. (13.) **Moench, G.**, and **Holt, H.**: Am. J. Obst. and Gynec., **22**, 199, 1931. (14.) **Vose, S. N.**: Urol. and Cutan. Rev., **34**, 826, 1930. (15.) **Williams, W. W.**, and **Savage, A.**: Cornell Veterinar., **15**, 353, 1925. (16.) **Woloskow, P. A.**: Pfobl. An. Husb., No. 2, p. 69, 1936 (in Russian).

VITAMIN C IN THE SPINAL FLUID.

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We[9a] have recently suggested that vitamin C may play a rôle in the metabolism of nervous tissue and presented the following evidence:

1. It is present in the cerebrospinal fluid.

2. The adrenal, brain and pars intermedia of the hypophysis (all nervous tissues) contain large amounts of vitamin C.

3. Clinical alcoholic conditions association with neural or mental changes have subnormal vitamin C levels in the blood and spinal fluid, whereas chronic alcoholics without neural or mental changes tend to have normal vitamin C levels in the blood and spinal fluid.[9b] Whether vitamin C is a major factor in these changes is not as yet clear and hardly seems likely. The findings do, however, suggest that there is a large nutritional factor in the production of nervous and mental changes in alcoholics.

4. Vitamin C has definite protective and therapeutic value in experimental poliomyelitis (Jungeblut[4a,b]).

5. Pathologically (Davison[1]), the peripheral nerves of animals placed on a vitamin C—free diet showed slight disintegration of myelin and on rare occasions, destruction of the axis cylinder. In addition, the various nerve cells, especially the anterior horn cells, showed vacuolization, liquefaction necrosis, swelling and pyknosis. He, however, noted similar changes in guinea pigs that were totally starved and was therefore unwilling to attribute the changes noted to avitaminosis C.

6. Guinea pigs deprived of vitamin C became nervous and apprehensive (Meyers and McCormick[5]). They responded violently to the slightest noise, running wildly about the cage until they fell exhausted. We have been able to confirm these results in every detail.

It would therefore seem a matter of paramount importance not only to study the metabolism of this vitamin in the brain, but to establish some standards for normality regarding the presence of this vitamin in the spinal fluid.

Methods and Materials. Determinations of vitamin C in both the blood and spinal fluid were carried out on 257 patients. Half of the patients were from the psychiatric wards (including 130 alcoholics previously reported) and the others were from the medical and neurologic wards. No attempt was made to group these cases diagnostically—they were all, however, afebrile. Because of the large number of alcoholics and because the patients at this hospital are in general drawn from the lowest income groups, subsisting usually on diets low in all vitamins, there is a very high incidence of subnormal nutritional states in our material.

The specimens of spinal fluid and oxalated blood from each patient were taken immediately to the laboratory and titrated by the method of Farmer and Abt.[2]

We have regarded 0.70 mg. % as the lower limits of normal vitamin C in the blood plasma. This is the figure given for this method by Farmer and Abt,[2] Wright,[10] and Greenberg, Rhinehart and Phatak.[3] Determinations made by us on 14 healthy medical students and internes ranged from 0.74 to 1.38 mg. %.

Plaut and Bulow have set as normal standards for spinal fluid the following figures for the 20- to 35-year-age group, 1.77 mg. %; 36- to 59-year-age group, 1.97 mg. %; 61- to 83-year-age group, 0.51 mg. %. They do not state, however, what their criteria of normality are.

In a previous paper we[7] attempted to establish normal limits for the vitamin C content in the spinal fluid. We regarded as normal in spinal fluid those patients who had both normal bloods and a normal response to the 5-hour urinary excretion test of Wright.[8]* Of 133 patients studied, 26 fulfilled these criteria. Their spinal fluids ranged from 1.82 to 4.18 mg. % of vitamin C. In the present paper, we have considered 1.82 mg. % as the lower limit of normal cevitamic acid content of the spinal fluid.

* Wright's test consists in determining the total 5-hour urinary excretion of vitamin C following an intravenous test dose of 1 gm. of crystalline cevitamic acid. A 5-hour excretion of 400 mg. or more of cevitamic acid is considered normal.

After we had submitted this paper for publication a new photoelectric method of titrating vitamin C was published.* The authors of this paper claim that the method of Farmer and Abt, used by us in titrating spinal fluid, yields figures for vitamin C that are too high. However, in a previous study,[7] we have shown that a close parallelism exists between our blood and spinal fluid figures. Therefore, although our absolute numerical figures for vitamin C in the spinal fluid may be incorrect, we feel that their relationship to our blood vitamin C values is correct, and that consequently our conclusions are valid.

Plaut and Bülow[6a,b] reported losses of as high as 90% of the reducing power of the ascorbic acid in the spinal fluid on standing 1½ hours at room temperature, but state that it retains three-fourths of its reducing power if acidified with 0.1 cc. of trichloracetic acid to each cubic centimeter of spinal fluid. In our own determinations, we found a consistent average loss of reducing power against sodium 2:6 dichlor-phenol-indophenol of only 10% in 1 hour without acidification and only a negligible loss if the spinal fluid were acidified immediately.

Results. In analyzing our material we have divided our patients on the basis of blood vitamin C levels into 3 groups: 1, *Normal*, with blood levels of 0.7 mg. % or more; 2, *Intermediate subnormal*, with a blood vitamin C level of 0.4 to 0.69 mg. %; and, 3, *Low*, with blood vitamin C of less than 0.4 mg. %.

In the normal blood group (Graph 1) there are 42 cases. Of these, the spinal fluid is normal (1.82 mg. % or more) in 36 (86%). The average spinal fluid for the group is 2.40 mg. % of vitamin C.

In the intermediate subnormal blood group (Graph 1) there are 64 cases. Of these, the spinal fluid vitamin C is normal in 30 (47%) and low (below 1.82) in 34 (55%). The average spinal fluid value for the whole group is 1.81 mg. %.

In the low blood group (Graph 2) there are 151 cases. Of those, the spinal fluid is low (below 1.82) in 137 cases (91%). The average spinal fluid value for the group is 0.97 mg. % of vitamin C.

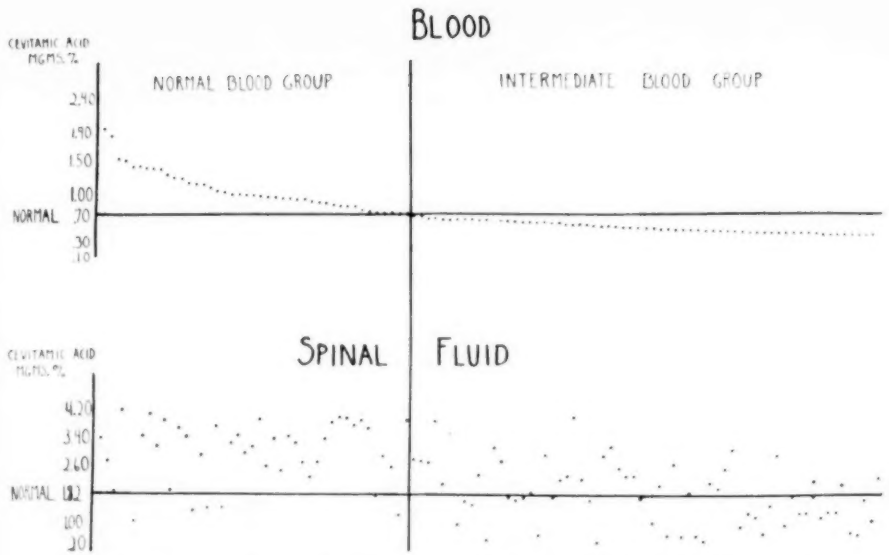
In Table 1, 248 cases in which the age was known are arranged by age groups (using the groupings of Plaut and Bulow).

Discussion. We believe that the results given above show that both a normal blood cevitamic acid (above 0.7 mg. %) and a very low blood vitamin C (below 0.4 mg. %) are almost invariably associated with correspondingly normal and subnormal values for the spinal fluid.

In the intermediate subnormal range no such close correlation exists. (In a previous paper[7] we demonstrated similar relationships with the urinary excretion test.)

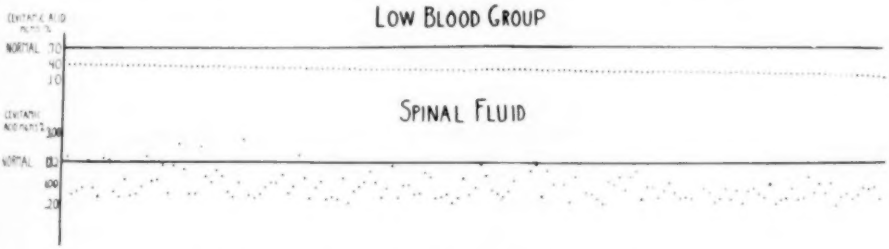
Our results show no significant age correlation in the level of vitamin C in the blood or spinal fluid. There is a slight drop in the

* Pijoam, M., Alexander, L., and Wilson, A.: J. Clin. Invest., **17**, 169, 1938.



GRAPH 1.—Spinal fluid correlations in patients with normal and moderately subnormal (intermediate) blood cevitamic acid.

This and the following graph are drawn in descending order of blood cevitamic acid. Each pair of dots on the same ordinate in the two halves of the graph represents simultaneous blood and spinal fluid determinations on the same patient.



GRAPH 2.—Spinal fluid correlations in patients with low blood cevitamic acid.

TABLE 1.—SPINAL FLUID CEVITAMIC ACID BY AGE GROUPS.

Age group.	No. of cases.	Spinal fluid vitamin C. (mg. %). Range.	Av. value.
0–19	5	0.92–4.18	1.74
20–35	69	0.46–3.96	1.59
36–60	138	0.36–3.96	1.54
61–83	36	0.28–4.07	1.27

TABLE 2.—NORMAL SPINAL FLUID CEVITAMIC ACID BY AGE GROUPS.

Age group.	No. of cases.	Spinal fluid vitamin C, av. value (mg. %).
0.19	2	3.73
20–35	21	2.92
36–60	49	2.64
61–83	7	3.05

spinal fluid cevitamic acid in the 61- to 83-year-old-age group. This is not present if only the normal spinal fluids are tabulated (Table 2). These findings are at variance with those previously reported by Plaut and Bülow[6a] and deserve further study.

Conclusions. 1. There is a close correlation between the blood and spinal fluid levels of vitamin C in the ranges stated.

2. There is no significant age correlation in the spinal fluid cevitamic acid of adults, although there is a slight drop in the group above 61 years of age.

3. It is probable that vitamin C plays a rôle in nervous tissue metabolism, although the mechanism of this action is not as yet determined.

We are indebted to Drs. Karl M. Bowman, Foster Kennedy and I. Ogden Woodruff for the use of clinical material from their respective services at Bellevue Hospital.

REFERENCES.

(1.) **Davison, C.**: Personal communication. (2.) **Farmer, C. J.**, and **Abt, A. F.**: Proc. Soc. Exp. Biol. and Med., **32**, 1625, 1935. (3.) **Greenberg, L. D., Rhinehart, J. F.**, and **Phatak, N. M.**: Ibid., **35**, 135, 1936. (4.) **Jungeblut, C. W.**: (*a*) J. Exp. Med., **62**, 517, 1935; (*b*) Personal communication. (5.) **Meyers, A. W.**, and **McCormick, L. M.**: Stanford Univ. Pub. Med. Sci., **2**, 747, 1927–30. (6.) **Plaut, F.**, and **Bülow, M.**: (*a*) Klin. Wchnschr., **13**, 1744, 1934; (*b*) Ztschr. f. d. ges. Neur. u. Psych., **152**, 324, 1935. (7.) **Wortis, H., Liebmann, J.**, and **Wortis, E.**: J. A. M. A. (8.) **Wright, I. S., Lilienfeld, A.**, and **MacLenathen, E.**: Arch. Int. Med., **60**, 264, 1937. (9.) **Wortis, H., Wortis, S. B.**, and **Marsh, F. I.**: (*a*) Arch. Neurol. and Psych., **39**, 1055, 1938; (*b*) Am. J. Psych., **95**, 891, 1938. (10.) **Wright, I. S.**: Am. J. Med. Sci., **192**, 719, 1936.

NOTE ON THE LACK OF CORRELATION OF CAPILLARY FRAGILITY WITH VITAMIN C CONTENT OF BLOOD, SPINAL FLUID AND URINE.

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At the present time, tests of capillary fragility are commonly used to determine the presence of "subclinical scurvy" associated with lowered vitamin C reserves. The reliability and actual relation of such tests as indices of vitamin C nutrition has been both affirmed[5,6,8,10,13,14,19] and denied[1,2,11,12] by various investigators.

In the course of studies on the relationship of vitamin C in the blood, spinal fluid and urine[16,17] we performed, in addition to chemi-

cal titration of the cevitamic acid, tests of capillary fragility on 88 patients on whom we had determined the blood vitamin C. In 78 of these the spinal fluid vitamin C was also determined and in 75 the urinary excretion following an intravenous test dose.

Methods. The capillary resistance and fragility was tested by two methods: 1, Wright's modification of the Rumpel-Leeds test;[19] and, 2, Dalldorf's suction cup method.[5] In all but 4 patients, who refused to coöperate in the rather uncomfortable Rumpel-Leeds test, both tests were done.

In Wright's modification of the Rumpel-Leeds test, a blood pressure cuff is applied to the arm and kept inflated for 15 minutes, one-half way between systolic and diastolic pressure. Five minutes after release of the cuff, the number of petechiæ in a 2.5 cm. circle drawn on the flexor surface of the forearm are counted. Wright considers 0 to 10 petechiæ normal and 10 to 20 borderline. For the sake of simplifying analysis, we have charted as "normal" all cases with 15 petechiæ or fewer.

In Dalldorf's method, a 1 cm. suction cup is applied to the skin of the upper arm near the deltoid insertion and varying negative pressures are applied for 1 minute. If petechial hemorrhage is produced at 25 cm. negative Hg pressure or below, the capillary fragility is regarded as abnormal (see discussion).

The vitamin C assays in the blood, spinal fluid and urine were done by the method of Farmer and Abt.[7] We regard as normal blood levels of 0.7 mg. % or over[2,7,9,16] and spinal fluid levels of 1.82 mg. % or over. After we had submitted this paper for publication a new photo-electric method of titrating vitamin C was published.* The authors of this paper claim that the method of Farmer and Abt, used by us in titrating spinal fluid, yields figures for vitamin C that are too high. However, in a previous study,[7] we have shown that a close parallelism exists between our blood and spinal fluid figures. Therefore although our absolute numerical figures for vitamin C in the spinal fluid may be incorrect, we feel that their relationship to our blood vitamin C values is correct, and that consequently our conclusions are valid. In studying the urinary excretion, the 5-hour test of Wright[20] was used in which in normal individuals 400 mg. or more of cevitamic acid are excreted in 5 hours following a 1 gm. intravenous test dose.

The patients used in this study were divided about equally between the neuro-psychiatric and general medical wards of this hospital. No attempt was made to select cases on a basis of either disease entities or dietary history. It should be noted, however, that the patients at Bellevue are in general drawn from the lowest income groups in the population and that consequently in our material there is a preponderance of low vitamin C levels.

Results. (See Charts 1 and 2.) To summarize, we find when the blood vitamin C is normal, the Rumpel-Leeds test is normal in about three-fourths of the cases (74%) and when the blood is either moderately subnormal or definitely low, the Rumpel-Leeds is abnormal in 70%. In other words, there is about 70 to 75% agreement between the blood vitamin C and the Rumpel-Leeds tourniquet test as standardized by Wright.

As the accompanying charts show, there was little correlation

* Pijoam, M., Alexander, L., and Wilson, A.: J. Clin. Invest., **17**, 169, 1938.

between Wright's modification of the Rumpel-Leeds test and the spinal fluid and urinary excretion assays of cevitamic acid.

If with the Dalldorf suction cup method 30 cm. Hg negative pressure is used as the lower limit of normal,* the test was found to have very little correlation with the actual vitamin assay.

As Charts 1 and 2 show, the incidence of "abnormal fragility" tests in the group of cases with normal vitamin C stores is too high and, conversely, the incidence of normal fragility in the cases with low vitamin C reserves is too frequent to make negative pressure tests, as used by us, of any clinical value.

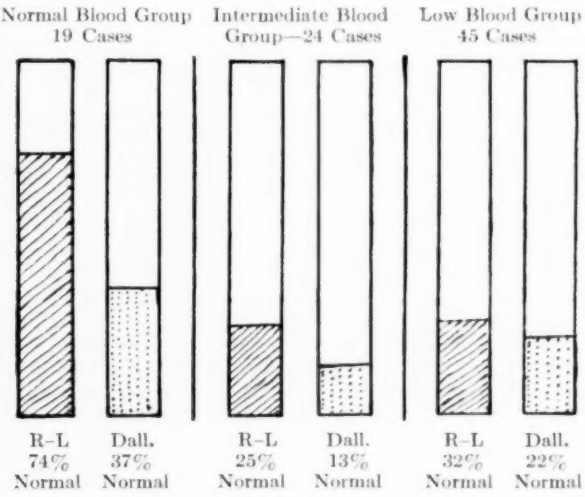

CHART 1.

It should be noted that both Wright and Dalldorf emphasize that single determinations are not of as much significance as a rise in the capillary resistance following vitamin C therapy. With this point of view we are in entire agreement. Dalldorf, indeed, in his published studies has never, except by implication, stated that there was any one level which could be taken as definitely abnormal. However, in a personal communication, he has stated that he believed a positive hemorrhagic reaction at 25 cm. Hg negative pressure probably was abnormal.

There was one observation that we made in using the Dalldorf

* We recalculated our results, using 20 cm. and 15 cm. of negative Hg pressure as lower limits of normal. Taking these values of normal, the results with the Dalldorf test are no better. For example, using 15 cm. Hg as the lower limit of normal, we find that there are 58% normal Dalldorf tests in the normal blood vitamin C group but that there then are (on this basis) 37% normal Dalldorf tests in the subnormal blood vitamin C group—a correlation still too poor to be of any clinical value. We also found that there was no significant change in the results if only tests with grossly confluent hemorrhage were considered as positive.

apparatus that we feel is worth mentioning. In 14% of our cases we found that with the suction cup a reaction that at lower negative pressures was positive, would be negative at high negative pressures, *e. g.*, hemorrhage could be produced at 35 cm. Hg negative pressure and not at 50 cm. We attribute this to complete shutting off of capillary flow at the rim of the cup at high negative pressures.

Finally, we wish to emphasize that there are other causes* than vitamin C deficiency of increased capillary fragility, and that abnormally high fragility should be attributed to vitamin C deficiency only if the vitamin C is low prior to therapy and if the abnormal state of fragility disappears following adequate vitamin C therapy.

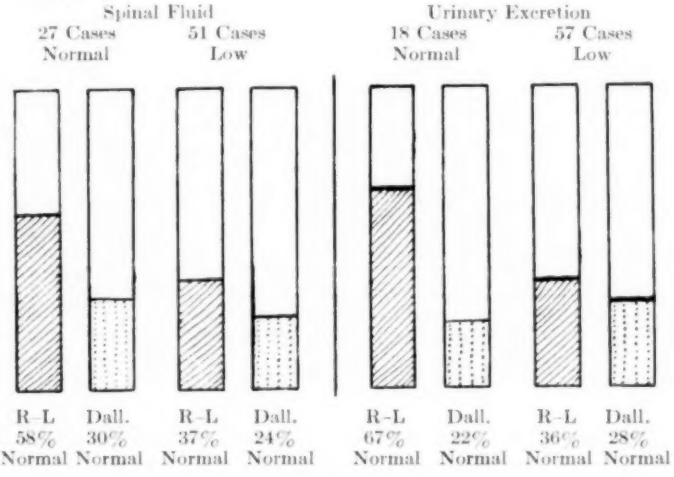

CHART 2.

Conclusions. 1. Clinical tests of capillary fragility may be normal in the presence of markedly low values for vitamin C in blood, spinal fluid and urine and conversely abnormal in the presence of normal C values.

2. The suction cup negative pressure method in our hands produced petechiæ at 25 cm. Hg in 63% of our normal cases and is, therefore, when used in this fashion, of little value in estimating vitamin C deficiency.

3. The Rumpel-Leeds test as standardized by Wright showed some correlation with blood vitamin C levels but not with spinal fluid or urinary excretion tests of vitamin C.

* The following other conditions have been listed as responsible for abnormal capillary fragility:[18] thrombocytopenic purpura, hemophilia, neoarsphenamine, and other drugs; anaphylactoid purpura, acute nephritis, carbon monoxide poisoning, toxins, *e. g.*, diphtheria, scarlet fever, acute infections; acetonia, menstruation, anemia, other vitamin factors, particularly vitamins P and D,[3,4,15] and a large group of cases in which the etiology is not apparent but which are certainly due to factors other than vitamin C.

4. If indirect methods of determining vitamin C must be used, Wright's modification of the Rumpel-Leeds test is the preferable method. The limitations of this test, however, must be understood.

5. Abnormal fragility tests should be considered as being due to vitamin C deficiency only if: *a*, the vitamin C in the body fluids is low; and, *b*, if the fragility returns consistently to normal following adequate vitamin C therapy.

We wish to thank Drs. I. Ogden Woodruff, Foster Kennedy, Karl M. Bowman, respectively, Directors of the First Medical, Neurological and Psychiatric Divisions of Bellevue Hospital for the use of clinical material from their wards.

REFERENCES.

(1.) **Abt, A. F., Farmer, C. J.,** and **Epstein, I. M.**: J. Pediat., **8**, 1, 1936. (2.) **Anderson, G. K., Hawley, E. E.,** and **Stephans, D.**: Proc. Soc. Exp. Biol. and Med., **34**, 778, 1936. (3.) **Bentsath, A.,** and **Szent-Gyorgi, A.**: Nature, **138**, 27, 1936. (4.) **Bentsath, A., Rusuyak, S.,** and **Szent-Gyorgi, A.**: Ibid., p. 798; **139**, 326, 1937. (5.) **Dalldorf, G.**: Am. J. Dis. Child., **46**, 794, 1933. (6.) **Dalldorf, G.,** and **Russell, H.**: J. Am. Med. Assn., **104**, 1701, 1935. (7.) **Farmer, C. J.,** and **Abt, A. F.**: Proc. Soc. Exp. Biol. and Med., **32**, 1625, 1935. (8.) **Gothlin, G. F.**: Skand. Arch. f. Physiol., **63**, 306, 1932. (9.) **Greenberg, L. D., Rhinehart, J. F.,** and **Phatak, N. M.**: Proc. Soc. Exp. Biol. and Med., **35**, 135, 1936. (10.) **Hess, A. F.,** and **Fish, M.**: Am. J. Dis. Child., **8**, 386, 1914. (11.) **O'Hara, P. H.,** and **Hauck, M. M.**: J. Nutr., **12**, 405, 1936. (12.) **Perry, C. B.**: Lancet, **2**, 426, 1935. (13.) **Schultzer, P.**: Ibid., **1**, 589, 1935. (14.) **da Silva-Mello, A.**: Münch. med. Wchnschr., **76**, 1717, 1929. (15.) **Weld, C. B.**: J. Pediat., **9**, 226, 1936. (16.) **Wortis, H., Liebmann, J.,** and **Wortis, E.**: J. Am. Med. Assn., **110**, 1896, 1938. (17.) **Wortis, H., Liebmann, J.,** and **Wortis, S. B.**: Am. J. Med. Sci., **196**, 384, 1938. (18.) **Wright, I. S.**: Ibid., **192**, 719, 1936. (19.) **Wright, I. S.,** and **Lillienfeld, A.**: Arch. Int. Med., **57**, 241, 1936. (20.) **Wright, I. S., Lillienfeld, A.,** and **MacLenathen, E.**: Ibid., **60**, 264, 1937.

NOTE ON THE LACK OF HEMOREGULATORY EFFECT OF ASCORBIC ACID ON PATIENTS WITH POLYCYTHEMIA VERA.

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It has been postulated by Barron that one of the functions of ascorbic acid is to maintain the hemoglobin concentration in the blood at its normal level. This hypothesis is supported by two facts. First, the decreased hemoglobin content in early stages of scurvy occurs before clinical symptoms appear; and the hemoglobin comes back to normal after the administration of ascorbic acid before these symptoms subside.[3,4] Second, cobalt polycythemia is prevented in rabbits when ascorbic acid and cobalt are given simultaneously.[1] Furthermore, ascorbic acid on oxidation reduces

ferrihemin to ferrohemin,[2] and hemoglobin results from the combination of ferrohemin and globin.

The power of ascorbic acid to control the appearance of cobalt polycythemia in rabbits suggested its use in the treatment of polycythemia vera. At Dr. Barron's suggestion, ascorbic was administered to several cases of polycythemia vera.

The first patient tested was an elderly man with a consistently high erythrocyte count and a peculiar violaceous color of his skin. He was treated while in the Billings Memorial Hospital, where he was on the service of Dr. G. F. Dick. There was some question about the correct diagnosis in this instance, so that the failure of the ascorbic acid to influence the erythrocyte count was more or less discredited. It was also felt at that time that if the erythrocyte count were brought down to normal levels the ascorbic acid might be more likely to maintain it there. Three such cases were then studied, brief synopses of which follow:

Case Abstracts. Case 1. A 50-year-old mulatto woman had been under treatment for 3 months for typical polycythemia vera, associated with hypertension. She had been given increasing doses of acetylphenylhydrazine hydrochloride until she was taking 0.2 gm. daily. After 10 days of this her erythrocyte count began to decline rapidly (Table 1) and she was hospitalized. As the blood count returned towards normal, the administration of 400 mg. of ascorbic acid daily was started. After 7 months there has been no apparent protection against the recurrence of polycythemia.

Table 1.—The Blood Picture in Case 1.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm.³	Comment.
2/23/37	26.2	9.30	Acetylphenylhydrazine
3/18	26.4	7.87	
4/1	26.2	9.24	No medication
4/15	24.2	7.99	
4/29	27.0	8.48	Acetylphenylhydrazine, 0.1 gm. b.i.d.
5/10	16.6	5.60	
5/15	....	....	Hospitalized
5/17	10.8	3.44	
5/24	8.3	2.99	
5/27	8.2	2.95	
6/3	10.6	3.49	
6/10	11.7	4.13	Ascorbic acid, 400 mg.
6/17	14.3	4.85	
6/24	14.9	4.90	
6/30	15.7	5.04	Discharged from hospital; vitamin C continued
7/13	16.2	5.20	
7/20	18.4	5.85	
12/	25.0	7.64	Ascorbic acid stopped

Case 2. A 57-year-old white woman had been under the care of one of us (E. V. K.) for 2 years for the control of classical polycythemia vera. At first, a solution of potassium arsenite was used satisfactorily, but when she became intolerant of it, acetylphenylhydrazine was given. At our suggestion she entered the hospital for experimentation. The dosage of acetylphenylhydrazine was increased steadily until the red blood count fell to just below normal (Table 2). At this time, 400 mg. of ascorbic acid was

given instead of the acetylphenylhydrazine. It is not possible to estimate any protection against the development of further anemia. After 4 weeks, because of a steady increase of the erythrocytes, the vitamin was discontinued.

TABLE 2.—THE BLOOD PICTURE IN CASE 2.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm.³	Comment.
6/4/34	22.4	6.57	Solution of potassium arsenite
10/16	18.0	5.33	
11/19/36	27.9	7.45	No drugs, 3 months
12/17	23.7	6.52	Acetylphenylhydrazine
2/13/37	....	4.20	
7/2	21.9	7.88	
7/5	....	....	Hospitalized, drug dose increased
7/8	24.3	7.69	
7/16	21.8	6.64	
7/26	21.6	5.97	
8/2	19.0	5.47	
8/9	16.3	5.01	
8/13	....	....	Ascorbic acid, 400 mg., replaces acetylphenylhydrazine
8/16	13.5	4.13	
8/23	12.0	3.45	
8/30	12.7	3.75	Discharged; vitamin C continued
9/16	18.2	4.97	Ascorbic acid stopped
9/20	20.2	6.33	Acetylphenylhydrazine
10/18	....	4.80	

CASE 3. A 46-year-old white man entered the hospital at our request for the management of an untreated case of typical polycythemia vera. His erythrocytes were decreased by daily venesection. A total of 4500 cc. of blood was removed in 6 days. Ascorbic acid was given in daily doses of 400 mg. after the second day in the hospital. Four weeks after the last bleeding the vitamin was discontinued because of a steady increase of the erythrocytes (Table 3).

TABLE 3.—THE BLOOD PICTURE IN CASE 3.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm.³	Comment.
9/2/37	26.4	8.35	
9/3	....	....	Hospitalized
9/4	22.0	9.00	Ascorbic acid, 400 mg., started; venesections started
9/7	20.7	6.79	
9/10	16.6	4.91	
9/11	....	....	Venesection stopped
9/13	15.0	4.85	
9/15	14.8	4.89	Discharged; vitamin C continued
10/5	16.4	5.72	Ascorbic acid stopped
10/21	18.2	6.50	Acetylphenylhydrazine
11/11	16.0	5.66	
12/16	15.2	5.19	

Two outpatients, suffering from characteristic polycythemia vera, whose blood counts had been well controlled by acetylphenylhydrazine, were given instead 400 mg. of ascorbic acid daily. Their blood counts promptly increased and the vitamin was withdrawn.

Summary and Conclusions. 1. An attempt has been made to discover whether ascorbic acid is capable of maintaining the erythrocyte counts of patients with polycythemia vera at normal levels.

2. Ascorbic acid seems to have no influence, either good or bad, on the red blood counts and the hemoglobin levels of such patients, especially in preventing the return to polycythemic levels.

REFERENCES.

(1.) **Barron, A. G.**, and **Barron, E. S. G.**: Proc. Soc. Exp. Biol. and Med., **35**, 35, 1936. (2.) **Barron, E. S. G., DeMeio, R. H.**, and **Flemperer, F.**: J. Biol. Chem., **112**, 625, 1936. (3.) **Dunlop, D. M.**, and **Scarborough, H.**: Edin. Med. J., **42**, 476, 1935. (4.) **Presnell, A. K.**: J. Nutr., **8**, 69, 1934.

RELIEF OF ANGINOID PAIN FOLLOWING REMOVAL OF INTRATHORACIC NON-TOXIC NODULAR GOITER.*

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Various aspects of the relationship between the thyroid gland and cardiac disorders have been studied and discussed in detail in the literature. These include: (*a*) the effect of total ablation of the normal thyroid upon congestive heart failure and angina pectoris; (*b*) the relationship between thyrotoxicosis and congestive heart failure, cardiac arrhythmias, and angina pectoris; and (*c*) the relationship between "non-toxic" goiter and certain cardiac abnormalities. One aspect of the general problem, however, has received comparatively little attention, namely the relationship between substernal "non-toxic" goiter and anginoid pain.

Bisgard[1] in 1936 reported the case of a 67-year-old man with a large nodular substernal goiter of long standing, who had exhibited effort angina for 2 years. The basal metabolic rate was −32%; glucose tolerance was somewhat impaired; blood cholesterol was 173 mg. %, and the electrocardiogram was normal. After subtotal thyroidectomy the attacks of pain disappeared promptly, the basal metabolic rate rose to normal, and glucose tolerance improved. Bisgard suggested that interruption of possible direct nervous communication between the heart and the thyroid, in the adventitia of the aorta, carotid, innominate or thyroid arteries, might have produced the relief of pain in his patient.

Kreuzfuchs[2] recently described what he calls "thyreoptotic pseudo-angina pectoris" and states that he had mentioned it as early as 1912. He believes that anginoid pain, without true heart disease, may be associated with "ptosis" of a normal thyroid isthmus or with intrathoracic goiter, especially in the fifth and six decades;

he ascribes the symptoms to pressure upon the aorta, or to displacement of the trachea and cardiac plexuses. He considers irradiation the treatment of choice,* but states that in some cases the symptoms subside spontaneously after the age of 50.

In connection with these reports, the following case is of interest.

Case Report. R. S., a married Jewish woman, aged 45, was first seen by one of us on November 13, 1935. She had been in good health, except for slight dyspnea on effort, until the evening of October 24, 1935. While sitting quietly at home, she was suddenly seized with a sense of tightness and pressure in the left upper chest, left shoulder, the left side of the back to the waist, the inner side of the left arm to the elbow and the left lower jaw. The sensation was extremely severe and did not start at one spot and radiate, but appeared simultaneously in the above mentioned areas, and was associated with difficulty in respiration. The symptoms lasted about 5 minutes and left her in a weakened condition. A few minutes later, she had another seizure of a similar nature, and her family physician was called. Except for a rise in blood pressure of 40 mm. Hg and tachycardia, nothing of significance was found on examination. There was no cyanosis, cough, hoarseness, sweating or chilliness associated with the attack. This seizure, however, lasted about an hour.

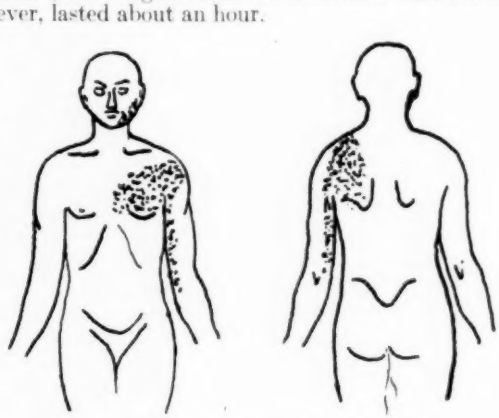
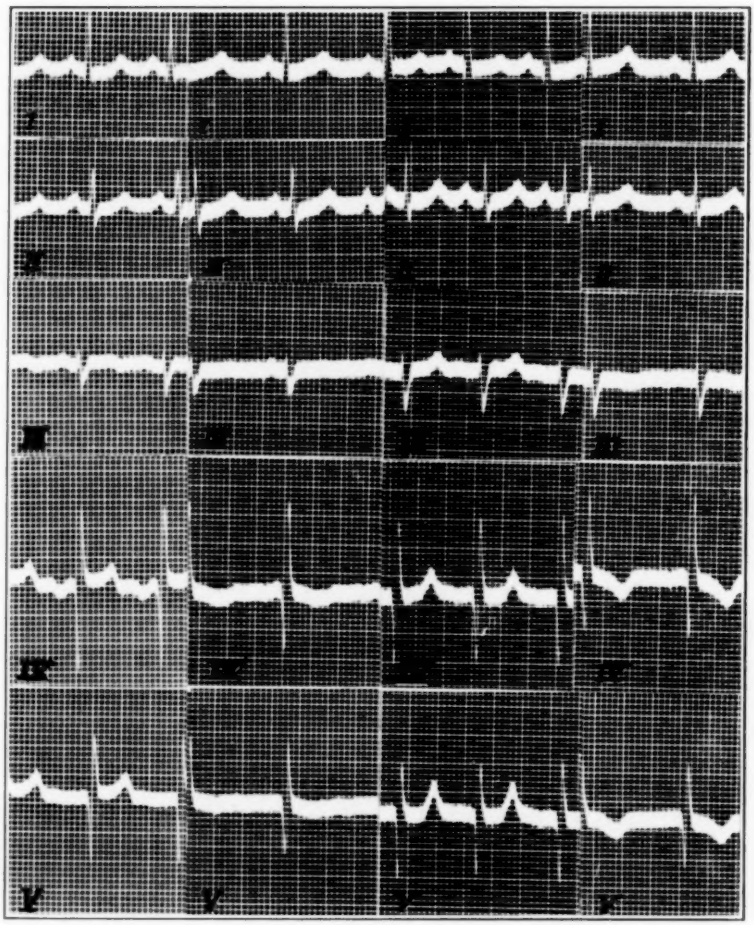


FIG. 1.—Distribution of pain during attacks.

During the following 3 weeks, the attacks recurred with great similarity of symptoms and time of onset. Usually, the seizures came on while at rest in bed, and awakened her from sleep between 4 and 5 A.M., whereupon she would get out of bed, walk about, and the attack would stop. One attack, however, lasted from 7 P.M. to 7 A.M. She was not aware of any exciting cause of the seizures; walking seemed to relieve the pain rather than induce it. Her past medical and family histories were unimportant.

On *physical examination*, she had the appearance of good health, was short and slightly overweight. There was no apparent dyspnea, cyanosis or jaundice. Her blood pressure was 120/80, and physical examination was negative except for diseased tonsils and dental caries. No thyroid enlargement could be detected in the neck. Fluoroscopy, however, disclosed a mass in the superior mediastinum, apparently substernal thyroid resting upon the aorta. The orthodiagram disclosed the heart to be of

* There is little evidence that the non-toxic thyroid is affected structurally or functionally by irradiation in therapeutic dosage.



A *B* *C* *D*

FIG. 2.—Electrocardiograms: (*A*) Before and after thyroidectomy. The only definite abnormality is the upright (pathologic) *T* waves in the precordial leads (IV and V). (*B*) Ten months after operation; at this time there was evidence suggestive of hypothyroidism. Note the flattening of the *T* waves in the precordial leads. (*C*) Fifteen months after operation; the attacks had recurred. The *T* waves in the precordial leads are again upright (pathologic). (*D*) Twenty-two months after operation and 4 months after last attack. The *T* waves in the precordial leads are inverted (normal). The precordial leads in all instances were taken with the right arm electrode at the fluoroscopic apex of the heart.

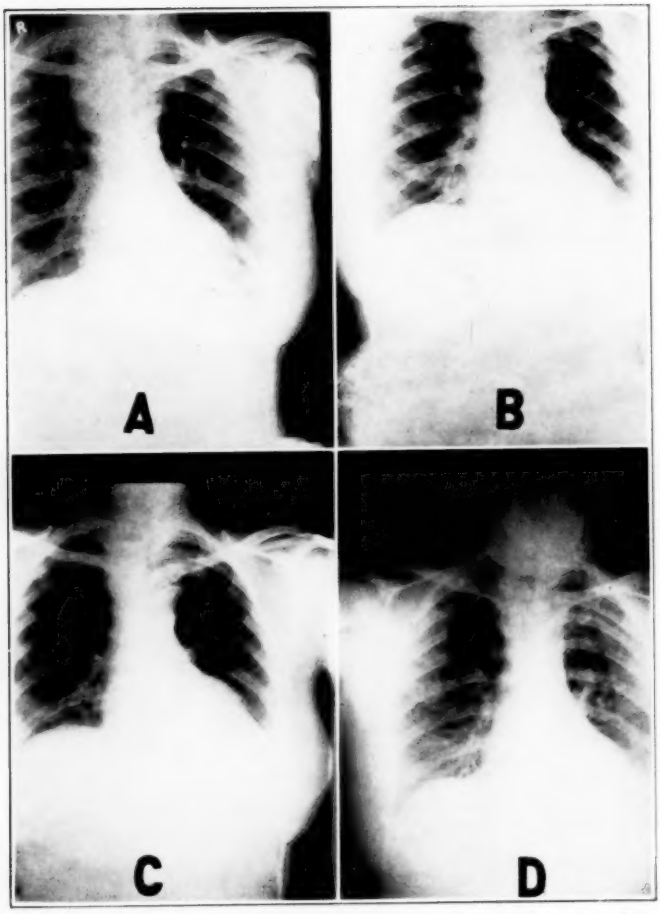


FIG. 3.—Roentgenographic appearance of the chest before and after thyroidectomy: (*A*) Before operation; note mediastinal mass, displacement of trachea of the left, and right scoliosis of cervical spine. (*B*) Two weeks after operation; mediastinal mass has disappeared but mediastinal shadow somewhat wide and dense; scoliosis and tracheal deviation still present. (*C*) Four weeks after operation; appearance essentially the same as *B*. (*D*) Twenty-one months after operation; mediastinum now seems normal. Scoliosis and tracheal deviation have now disappeared.

normal size, shape and position. The electrocardiogram showed upright (pathologic) *T* waves in the precordial leads; the limb leads were essentially normal (Fig. 2, *A*.)

She was admitted to the Medical Division of this hospital on November 16, 1935. Roentgen ray of the chest (Fig. 3) revealed the following: "The trachea is deviated considerably to the left by a substernal mass which is in the right upper thoracic region. The esophagus was also deviated to the left side. On swallowing, the mass went up into the neck and there was nothing to suggest an aneurysm of the innominate artery. The lung fields were clear. Diagnosis: Substernal extension of the thyroid on the right side producing tracheal deviation." Repeated electrocardiograms showed upright (pathologic) *T* waves in the precordial leads; the limb leads were essentially normal. Her basal metabolic rate was −9%. The blood count was normal. The blood urea nitrogen was 14 mg., sugar 90 mg. and cholesterol 250 mg.%. The urine was normal. Her blood Wassermann test was negative.

Attacks of pain occurred during the night but were not as frequent or severe as those experienced at home. All were relieved by nitroglycerin. It was decided to try the effects of Roentgen ray therapy and iodides, although no great change was anticipated if the mass were substernal thyroid. On December 5, 1935, Roentgen ray therapy was begun. Following each treatment, the seizures were more frequent and of increased intensity. After 5 daily treatments, during which a total of 1050 R was given, Roentgen ray of the chest showed no diminution in the size of the mass, although the roentgenologist considered the amount of treatment insufficient. Ten minims daily of a saturated solution of potassium iodide was given from November 28 until December 24, without apparent effect. The patient, refusing operation, left the hospital December 24, 1935.

The patient later consented to operation, performed January 22, 1936, by Dr. B. Lipshutz. The thyroid was found to be for the most part beneath the sternum, occupying the upper mediastinum, chiefly on the right side and adherent to the surrounding structures. The exact relation of the thyroid mass to the aorta could not be determined at the time of operation, although the Roentgen ray suggested a close approximation between them. With great difficulty, the gland was freed by finger dissection and a subtotal thyroidectomy performed. The dead space left in the uppper mediastinum was filled with narrow gauze packing. The portion of the gland removed weighed 80 gm. *Histologic examination*, by Dr. David Meranze, showed two distinct pictures: areas of essentially normal thyroid, and areas showing acini greatly distended and distorted with faintly staining colloid substance. In the colloid areas the acini varied greatly in size, some apparently having fused. Their lining cells were extremely flattened and the contained colloid stained palely. Some acini were hemorrhagic and some were replaced entirely with hyaline material showing acicular spaces and lipoid-filled cells.

Except for a cough, convalescence was uneventful and the patient was discharged from the hospital on February 4, 1936. The basal metabolic rate on February 4, 1936, was +15% and a Roentgen ray of the chest on the same day showed the absence of the previously reported supracardiac mass; the trachea continued somewhat compressed and displaced to the left, although less than before operation. The mediastinal shadow was still somewhat widened and abnormally dense. An electrocardiogram was not done.

When seen again, February 19, 1936, she reported several attacks of moderate pain of short duration. The electrocardiogram was essentially the same as before operation. On October 17, 1936, she complained of marked shortness of breath and sluggishness. The attacks, however, had

become increasingly infrequent. She had gained 36 pounds in weight since operation. The electrocardiogram (Fig. 2, *B*) showed flat *T* waves in the precordial leads. Her basal metabolic rate was −5% and blood cholesterol was 284 mg.%. She was placed on ¾ grain of thyroid substance (Armour) daily and on November 14, 1936, reported that she felt much better in general and that the attacks had been very infrequent and not severe. She had lost 5½ pounds in weight. In the middle of December, 1936, she stopped taking thyroid. She was comparatively free of symptoms until February 1, 1937, when she developed an acute bronchitis which was accompanied by a sense of thoracic pressure but no pain. On April 28, 1937, she had a recurrence of the attacks. (Fig. 2, *C* shows the electrocardiogram on that day.) She was placed on 1½ grains of thyroid substance daily which she took for 2 weeks. On October 12, 1937, she reported that she had not had any attacks except for a minor one in June. The electrocardiogram (Fig. 2, *D*) on that day showed inverted (normal) *T* waves in the precordial leads for the first time since she came under observation. (Fig. 3, *D* shows the Roentgen ray of the chest taken the same day.) Her basal metabolic rate on October 18, 1937, was +5% and the blood cholesterol was 403 mg.%. She was last seen on May 28, 1938, when she reported that she had had no further attacks since the slight one in June (about 11½ months) and was feeling well in general.

Comment. Several features require comment. First, although relieved by nitroglycerin, the attacks of pain were nocturnal, and were not precipitated by exercise; indeed, at times exertion brought relief. Second, removal of the substernal goiter was not followed by immediate disappearance of the attacks; they continued to recur, though at infrequent intervals, for about 17 months after operation. Third, a scoliosis of the cervical spine to the right is apparent in the Roentgen rays taken before operation. This, together with the tracheal deviation, persisted for at least 1 month after operation. Some increase in width and density of the upper mediastinal shadow was also noted for the same length of time. All these findings had disappeared in the film made 21 months after operation, when the attacks had ceased. Fourth, the hypercholesteremia suggested some thyroid deficiency before operation (although the basal metabolic rate was not in conformity with this), and the picture was even more suggestive of hypothyroidism 9 months after operation. Finally, the electrocardiographic changes might have been associated with the goiter regardless of its location, as it has been shown that "non-toxic" goiter may be associated with a variety of electrocardiographic abnormalities (in limb leads at least) and that they may disappear at varying intervals after the removal of such goiters.[4]

Discussion. Several possible explanations for the relief following thyroidectomy may be considered.

1. A state of myxedema comparable to that produced by total thyroidectomy might have been produced. This is supported by the patient's appearance and the hypercholesteremia 9 months after operation. It is contradicted, however, by the basal metabolic rate and by her present appearance.

2. On the contrary, the coronary circulation might have improved following the removal of a mass of non-functioning thyroid tissue, a state of thyroid insufficiency having been thereby corrected. This possibility is eliminated by the marked hypercholesteremia found in October, 1937. Furthermore, the original attacks of pain were not of the type usually seen in persons with coronary artery disease.

3. Afferent nerve pathways contained in the vagus branches, the superficial or deep cardiac plexuses, a plexus in the upper posterior mediastinum,[3] the superior or middle cardiac nerves, or ramifications thereof, may have been interrupted by the operation. Weinstein and Hoff[5] have confirmed the intimate relationship between the superior and middle cardiac nerves and the sympathetic innervation of the thyroid. Subtotal thyroidectomy could thus have easily interrupted sensory impulses traveling through the superior or middle cardiac nerves.

4. Part of the intrathoracic thyroid mass may have produced the pain by pressure upon the periaortic part of the superficial cardiac plexus, and relief of this pressure by the operation may have relieved the pain. Both this and the preceding hypothesis, however, leave the electrocardiographic changes and the postoperative recurrences of pain unexplained.

5. The possibilities that the entire symptom complex may have been functional, or that the subsidence of the attacks bore no relation to the thyroidectomy, seem too remote to require discussion.

It would appear that no entirely satisfactory explanation can be offered of the mechanism whereby relief of the pain in this case followed removal of the intrathoracic goiter. The persistence of the cervical scoliosis and tracheal deviation for at least 1 month after operation suggests the possibility of some residual exudate or inflammatory process in the bed of the mediastinal goiter, which might have been a factor in the postoperative recurrences of pain. The tracheal deviation may have played a part in the production of the attacks,[2] although dyspnea was not a symptom. From Bisgard's[1] report and our own experience, it seems justifiable to conclude that intrathoracic goiter, without the usual phenomena of hyperthyroidism, may be associated with typical angina pectoris or anginoid chest pain, and that relief may follow removal of the goiter.

Summary. The case is reported of a 45-year-old woman who suffered repeated severe attacks of thoracic and shoulder pain, who also presented electrocardiographic abnormalities, hypercholesteremia, and a large intrathoracic goiter in proximity to the aortic arch. Subtotal thyroidectomy was followed by marked reduction in the frequency and severity of the attacks, and eventually by their disappearance (for 11½ months up to the time of writing) and by the return of the electrocardiogram to normal.

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Since the above was written attention has been called (Reid, W. D., J. Am. Med. Assn., **110**, 1724, 1938) to thoracic pain following compression of the brachial plexus by cervical rib or the scalenus anticus muscle, and a case cited in which such pain disappeared after correction of a left scoliosis. This suggests another possible explanation for the events in our case, *i. e.*, the goiter may have given rise to the right cervical scoliosis which in turn may have caused tension of the left scalenus anticus with brachial plexus compression, the syndrome being terminated by removal of the goiter and subsequent disappearance of the scoliosis. This would not, however, explain the electrocardiographic changes (see Fig. 3).

REFERENCES.

(1.) **Bisgard, J. D.**: J. Am. Med. Assn., **106**, 1639, 1936. (2.) **Kreuzfuchs, S.**: Wien. klin. Wchnschr., **49**, 1314, 1936. (3.) **Mayne, W.**, and **Katz, L. N.**: Am. J. Physiol., **114**, 688, 1936. (4.) **Rose, E., Wood, F. C.**, and **Margolies, A.**: J. Clin. Invest., **14**, 497, 1935. (5.) **Weinstein, A. A.**, and **Hoff, H. E.**: Surg., Gynec. and Obst., **64**, 165, 1937.

ISOLATED CALCIFIED AORTIC STENOSIS.

WITH PARTICULAR REFERENCE TO ITS ETIOLOGY AND DIFFERENTIAL DIAGNOSIS.

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ALTHOUGH calcification of the aortic valve has received considerable attention during the past few years, its importance clinically is not generally appreciated. The early literature contains a few references to this lesion. As far back as 1672 Rayger[3] described an autopsy in which there was "osseous fusion of the aortic cusps." In 1706, Cowper[10] described a case with "petrifaction of the stenosed semilunar valves of the left ventricle." However, the first extensive study of this lesion was made by Mönckeberg in 1904.[15] Interest in this particular condition has been revived recently by the pathologic studies of Margolis, Ziellessen and Barnes[12] and by Christian[6] who accurately described the clinical picture. Sosman and Wosika[16] outlined the roentgenologic technique for demonstration of calcified valves and reported 12 cases diagnosed during life. Willius and Camp[18] discussed 15 cases diagnosed during life. Though Blackford, Bryan and Hollar[1] could find less than 50 cases of calcification of the aortic valve in the literature diagnosed during life, autopsy studies indicate that this lesion is not uncommon. Clawson[7] found that in 253 deaths from lesions of cardiac valves, the aortic valve was calcified in 93. White and McGinn[11] state that 1.8% of routine autopsies and 2.3% of cardio-vascular cases show this lesion.

Clawson, Noble and Lufkin[9] found that the aortic valve was involved in 54% of their total number of healed valve deformities.

Material. This study is based upon autopsy protocols of 9123 consecutive postmortem cases from three hospitals in Saint Louis (City Hospital No. 1, Jewish and Barnes) and 13,000 autopsies at Johns Hopkins Hospital;* a total of 22,123 autopsies. We were primarily interested in those cases showing pure aortic stenosis without involvement of other valves or chordæ tendineæ that would obviously suggest rheumatic fever as the etiologic agent. There were 72 such cases in this series. Only those cases showing at least a moderate degree of aortic stenosis were included in this study. A large number of cases with isolated sclerotic plaques on the aortic valve leaflets were not included, since no apparent stenosis was present. In 19 of the 72 cases, there was a co-existing arteriosclerotic involvement of the mitral valve, with marked calcification chiefly at the base of the valve. In none of these 19 cases was there any evidence of rheumatic involvement of the mitral valve.

In the 13,000 autopsies at Johns Hopkins Hospital there was a total of 89 recorded cases of aortic stenosis; occurring as an isolated aortic lesion in 24 and with combined involvement of other valves or chordæ tendineæ in 65. Those cases in which rheumatic fever was an etiologic agent almost without exception showed some involvement of the mitral valve. Among the rheumatic fever cases only 1 lived to be over 40. His death at the age of 43 raised the average age of death in this group from 22 to 24.

Analysis of the combined autopsy records, clinical histories and available gross and microscopic specimens of the cases of isolated aortic stenosis gave the following results.

Incidence. Seventy-two cases in 22,123 routine autopsies (0.32%).

Sex. Sixty-five (90%) of the 72 cases were males.

Age. The average age of the group was 60.5 years; 8 cases were under 50, 10 under 40. The youngest patient in this group was 32 years of age and the oldest 93.

Rheumatic History. Only 3 cases gave a definite history of acute rheumatic fever. One of these, who died at the age of 39, gave a history of acute rheumatic fever at ages of 23 and 25. At autopsy, the aortic valve showed moderate calcification, while the mitral valve was free of involvement. Another patient, who had acute rheumatic fever at 16 years and died at 34, at autopsy showed a thickened and fused aortic valve with minute fresh vegetations at the edges, some of which were calcified. It is felt that the history of rheumatic fever is unreliable—whether taken from hospital records or obtained from the patient. Previous attacks are often overlooked and may have been unrecognized. However, it is obvious that a positive rheumatic history in cases of isolated calcareous aortic stenosis is extremely uncommon.

Syphilis. Three cases had positive serologic tests, but there was no evidence recorded of luetic aortitis, grossly or microscopically.

Blood Pressure. In the 48 Saint Louis cases with records of blood pressure the average systolic pressure was 140, diastolic 67. The systolic pressure was over 160 in 9 cases and under 100 in 6; 5 patients had diastolic pressures below 60. The average pulse pressure of the group was 73. Six had a pulse pressure over 100. These figures show that approximately 87% of aortic stenosis cases will have a normal or decreased pulse pressure.

* It so happens that the first recorded autopsy at the Johns Hopkins Hospital was on a case of aortic stenosis combined with a vegetative and ulcerative endocarditis in a man, 68 years of age. The bacterial nature of the acute lesion was of course not studied. The upper portions of the valve leaflets are described as thickened and indurated.

In the Saint Louis series of 9123 cases there were 104 cases of luetic aortitis (an incidence of 1%). Four cases died so soon after admission to the hospital that no tests could be made. Of the remaining 100 cases, 93 had positive serologic tests; 6 were negative. In 1 case the blood Kahn and Wassermann tests were negative, while the spinal fluid Wassermann was positive. A microscopic diagnosis of luetic aortitis was made in each case. Several cases, previously diagnosed as luetic aortitis with negative serologic tests, were found to be purely arteriosclerotic on closer examination of the sections and were excluded. This indicates a higher incidence of positive blood tests in luetic aortitis than is generally reported. While definite cases of luetic aortitis with negative tests do occur, the diagnosis of luetic aortitis in the presence of a negative blood Kahn and Wassermann must be made with extreme caution, especially if it remains negative following a provocative test.

Clinical Course. The clinical picture of calcification of the aortic valve has been accurately described by Christian[6] and more recently by Willius and Camp.[18] The typical case is that of a male over 50 years, with the usual history of cardiac decompensation, a to and fro murmur or absent second sound with a thrill over the aortic area, a normal or decreased pulse pressure and a negative blood serology. Of course, some cases do not entirely fit this picture. There may be few symptoms referable to the heart and the stenosis is usually of long duration and marked in degree before signs of heart failure appear. In the presence of hypertension or a marked aortic stenosis with retraction of the cusps, the pulse pressure is increased. Although most of these cases terminate with the usual course of cardiac failure, death may occur very suddenly as described by Marvin and Sullivan.[14] Boas[2] stresses the relationship of angina pectoris, heart block and aortic stenosis.

The physical findings can be clearly explained by the pathologic process. The signs are usually those of a stenosis with slight aortic insufficiency, in contrast to the free regurgitation and no stenosis of luetic involvement of the aortic valve. The calcification in aortic stenosis affects the valve leaflets and the base of the valve, but very rarely extends on to the aortic wall, so that there is no dilatation of the aortic ring. Usually the aortic wall in the proximity of the valve is remarkably free from atheroma. In syphilis, the essential lesion is a destruction of the media of the aortic wall and as it progresses toward the aortic ring produces dilatation and consequent signs of a free regurgitation. There is no impediment to the flow of blood in a luetic aortitis.

Case Reports. Some of the difficulties encountered in diagnosis are illustrated in the following cases:

Case 1.—W. D., a white male, aged 53, entered the hospital irrational and in a critical condition. A history of antiluetic treatment for the past 4 years was obtained from his wife. His record showed a negative Wassermann and a 2+ Kahn test at the onset of antiluetic treatment. He was treated as a case of latent lues with bismuth and mixed treatment. Serologic examinations during the next 4 years were all negative and 2 spinal punctures were negative. On admission, the heart was enlarged; the

rhythm regular. There was a loud harsh systolic murmur heard over the aortic area. The aortic second sound could not be heard. There was a soft systolic murmur at the apex. No thrill was felt. There was no widening of the supracardiac dullness on percussion. The blood pressure was 95/72. There was no edema. The remainder of the examination was negative except for generalized arteriosclerosis. The Kahn test was negative. W.B.C. 12,500; R.B.C. 4,800,000; Hb. 80; urine showed moderate amount of albumin with an occasional cast; NPN 30; sugar 92; spinal fluid was normal.

The *clinical diagnosis* was syphilis of the central nervous system and aortic stenosis or luetic aortitis. The patient expired 4 days later.

At *autopsy* there was a marked calcified stenosis of the aortic valve. The other valves were normal. There was a generalized arteriosclerosis. There was no evidence of luetic aortitis.

The picture that this patient presented was typical of a calcareous aortic stenosis.

Case 2.—K. G., a white female, aged 54, entered the hospital complaining of generalized weakness, dyspnea, and precordial pain. She had been in the hospital 1 year previously and had been diagnosed as a case of luetic aortitis. The essential physical findings were: irregular pupils which reacted sluggishly to light; moist râles in bases of the lungs and slight peripheral edema; the heart was enlarged. A to and fro murmur was heard over the aortic area and a soft systolic murmur at the apex. The blood pressure was 200/60 and a generalized arteriosclerosis was present. The Kahn and Wassermann reactions were 4+ positive. NPN 19; sugar 77; W.B.C. 7200; R.B.C. 3,200,000; Hb. 70%; urine was normal. The electrocardiogram showed evidence of myocardial lesions or digitalis effect with ventricular extrasystoles.

The *clinical diagnosis* was luetic aortitis with aortic regurgitation. She was digitalized with slight temporary improvement and expired 3 weeks later.

At *autopsy* there was no evidence of a luetic aortitis, either grossly or microscopically. The aortic valve showed marked calcification involving the entire aortic ring. The other valves were remarkably free from involvement. There was a generalized arteriosclerosis.

Case 3.—A. F., a white male, aged 49, entered the hospital complaining of dyspnea, precordial pain and edema of 3 months' duration. On examination, the heart was enlarged and there was a loud harsh systolic murmur and a soft diastolic murmur heard over the aortic area and a soft systolic murmur over the mitral area. The blood pressure was 180/65. There was a peripheral edema. The Kahn reaction was negative. Urine showed moderate albumin. W.B.C. 10,600; R.B.C. 4,700,000; Hb. 80; NPN 31; sugar 92. The electrocardiogram showed auricular fibrillation and ventricular extrasystoles.

The *clinical diagnosis* was luetic heart disease with aortic regurgitation and decompensation.

At *autopsy* there was no evidence of a luetic aortitis, either grossly or microscopically. The aortic valve showed marked calcification and stenosis. There was also a generalized arteriosclerosis.

Etiology. There has been considerable controversy regarding the etiology of isolated aortic stenosis and the question is still far from settled. Various workers believe that it is the result of an inflammatory involvement of the valve, such as rheumatic fever or bacterial endocarditis; others maintain that the lesion is purely non-inflammatory—the result of a degenerative metabolic process.

Others believe that either or both causes may be active, while still others hold that the etiology of the lesion is entirely unknown. Mönckeberg,[15] in 1904, studying aortic valves in which there was extensive calcification, decided that the process in the cusps was the same as that found in the intima of the aorta in senile arteriosclerosis. Margolis, Ziellessen and Barnes[12] and Clawson, Bell and Hartzell[8] believe that some of these cases represent a non-inflammatory degenerative process. Clawson,[7] in an analysis of Mönckeberg's work, stated that there was no support for the metabolic theory of the structural changes in these valves and he thought that an infectious basis was more probable. Christian[6] and Clawson, Noble and Lufkin[9] believe that rheumatic fever is the cause. Cabot[5] suggests that the lesion may follow bacterial endocarditis. Mallory[13] believes that this lesion is rarely rheumatic in origin.

The question of etiology is obviously difficult: for instance, most of the cases as seen at autopsy present the final stages of a process without any clue as to its origin. The variance of opinion among experienced authors about this question would suggest that no one factor is the sole etiologic agent for the entire group. There are good arguments for and against each of the various theories proposed.

In *acute rheumatic fever* the involved valve becomes swollen and thickened and small bead-like vegetations form along the line of contact of the valve. Boyd[4] stresses that the essential valvular lesion in acute rheumatic fever is an inflammation of the entire valve, a valvulitis, and that the vegetations are to be regarded as merely incidental: there are Aschoff bodies and an increased number of fibroblasts; the chordæ tendineæ and wall of the auricles are often affected. In the healing stages, fibrous tissue forms to produce dense scar tissue. In later years, lime salts may be deposited to produce calcification or even true bone. Boyd[4] also states that in every case of rheumatic carditis, the mitral valve is injured.

The main lesion in the healed rheumatic valve is fibrosis. If there is a co-existing involvement of the mitral valve with thickening and fibrosis, or involvement of the chordæ tendineæ, the etiology is rheumatic. In an isolated aortic lesion, with a normal mitral valve, fibrosis and thickening of the edges of the cusps, indicate that the etiology is probably rheumatic. On the other hand, if the valve shows a sclerotic base with calcified nodules scattered over the valve and the remainder of it is thin and not fibrosed, the lesion is probably arteriosclerotic. White[17] states that when the entire valve is calcified with retraction and marked stenosis, Mönckeberg's sclerosis alone is not to blame, but rather a combination of the old infectious process and superimposed calcification.

The occurrence of a calcareous lesion in the aortic valve alone, without involvement of the other valves is important but not conclusive evidence against a rheumatic etiology, because the proven rheumatic aortic lesion usually has associated mitral damage.

Further evidence against a rheumatic etiology is the large incidence among males and the advanced age at death (90% males and average age of 60 years in our series). White[17] states that rheumatic fever affects females more commonly than males in the ratio of about 5 to 4 or 4 to 3.

Aortic stenosis of rheumatic origin, however, becomes calcified relatively early, and only a few cases are seen at autopsy with a pure fibrotic lesion. The stenosed rheumatic mitral valve consists of a thickened fibrous hyalinized mass and calcification is unusual except in very old individuals. It seems strange that the course of this lesion in the two valves in such close proximity is so different. Another interesting observation is that in most of the cases of calcified aortic stenosis the proximal portion of the aorta is relatively free of atheroma.

In valvular *arteriosclerosis* of the atherosclerotic type, subendothelial fatty deposits and fibrosis precede deposition of lime salts. The process can affect any portion of the valve, but is more common at the base of the valve. The earliest example of this process was seen in a recent autopsy, in which there was a small lesion on one of the aortic cusps. The mitral valve was entirely normal as were the other two aortic cusps. The lesion was located near the base of the valve, about 5 mm. in diameter on the aortic side, was well localized and showed early calcification. The remainder of the valve was smooth, thin and entirely normal. The aorta showed marked arteriosclerosis. This lesion certainly appeared degenerative and it is highly improbable that it could be the result of an inflammatory process. Progression of the lesion and the formation of similar areas on the other aortic cusps would in time undoubtedly produce a typical calcified aortic stenosis. While there is usually an accompanying arteriosclerosis of the aorta, this is by no means constant.

There seems to be relatively little in the literature regarding the rare arteriosclerotic involvement of the mitral valve. It seems fairly definite that this process affects primarily the base of the valve with degeneration and later calcareous deposits. This produces a calcified bar around the base of the valve, leaving its edges remarkably free. It is unusual for the process to become so extensive that the entire valve leaflets of the mitral valve are involved by these calcareous deposits, except in very old patients. The same process usually extends on to the aortic valve which lies in close proximity.

An uncomplicated luetic aortic valvulitis is usually accompanied by luetic aortitis and rarely calcifies. However, neither of these criteria always maintains.

So it would appear that no one etiologic factor is responsible for all cases of calcification of the aortic valves. Sometimes the lesion is inflammatory, sometimes degenerative and in still other cases both processes are probably present. Careful examination of the affected

valve and the appearance of the other valves, particularly the mitral, will often indicate the probable etiology. In cases of isolated aortic stenosis, arteriosclerosis is usually the cause. However, it is often impossible to determine the etiology in a far-advanced aortic stenosis.

Diagnosis. The clinical diagnosis of calcareous aortic stenosis should not be difficult if the condition is kept in mind. The various characteristics of the clinical course have been discussed, which are primarily the signs of an aortic stenosis with slight regurgitation in an old person with a negative serology. A valuable aid in the diagnosis of this lesion is the Roentgen ray, according to the technique described by Sosman and Wosika.[16] They were able to diagnose a large percentage of these cases by the use of the fluoroscope and Roentgen ray films. This method of examination has been of definite value, if there is a fair degree of calcification present. Fluoroscopic examination, showing the characteristic movements of the calcified valve with each heart beat, is more reliable than the Roentgen ray films. It must be remembered that a special technique is necessary to visualize these valves on a film, since the ordinary routine Roentgen ray of the heart will not show calcification within the heart.

Luetic aortitis frequently enters into the differential diagnosis. If the classical signs of both lesions are carefully considered, the diagnosis should not be difficult. However, in some cases (such as those presented) the diagnosis may be very difficult, particularly if serologic tests are positive and the pulse pressure is elevated. At present there is a general tendency to diagnose luetic aortitis rather freely, regardless of the blood serologic tests. The diagnosis of a luetic aortitis with negative serologic tests should be made with great caution, for it entails a tedious and expensive treatment and offers an entirely different prognosis. If there are signs of an aortic regurgitation and the blood serologic tests are negative, the possibility of an aortic stenosis must be carefully considered. The frequent teaching that a to and fro murmur over the aortic area, in the absence of mitral involvement, is invariably syphilitic is certainly not true.

Conclusions. 1. Isolated calcareous aortic stenosis has a characteristic clinical and pathologic picture.

2. A study of 72 cases of isolated aortic stenosis found in 22,123 consecutive postmortem examinations is presented.

3. There were 104 cases of luetic aortitis in 9123 autopsies in the Saint Louis group.

4. The etiology of calcareous aortic stenosis seems impossible to decide with certainty. It is believed that in isolated aortic valve involvement, arteriosclerosis is the usual cause, but it can also result from an inflammatory process and in some cases from both.

5. The diagnosis can be made in most cases if the clinical characteristics and the possibility of a calcareous aortic lesion are kept in mind. The fluoroscopic and Roentgen ray methods of examina-

tion of the heart valves are of definite value and should be more commonly utilized.

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REFERENCES.

(1.) **Blackford, L. M., Bryan, W. W.,** and **Hollar, E. D.**: J. Am. Med. Assn., **107**, 18, 1936. (2.) **Boas, E. P.**: Am. J. Med. Sci., **190**, 376, 1935. (3.) **Bonet, T.**: (Quoted by in 1679) Sepulchretum sive Anatomica Practica, Geneva, Cramer and Perachon, **1**, 891, 1700 (1st Ed., 1679). (4.) **Boyd, W.**: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 2d ed., p. 10, 1935. (5.) **Cabot, R. C.**: Facts on the Heart, Philadelphia, W. B. Saunders Company, p. 767, 1926. (6.) **Christian, H. A.**: J. Am. Med. Assn., **97**, 158, 1931. (7.) **Clawson, B. J.**: Arch. Path., **12**, 889, 1931. (8.) **Clawson, B. J., Bell, E. T.,** and **Hartzell, T. B.**: Am. J. Path., **2**, 193, 1926. (9.) **Clawson, B. J., Noble, J. F., Lufkin, N. H.**: Am. Heart J., **15**, 58, 1938. (10.) **Cowper, W.**: Phil. Trans., London, **24**, 1970, 1706. (11.) **McGinn, S.,** and **White, P. D.**: Am. J. Med. Sci., **188**, 1, 1934. (12.) **Margolis, H. M., Ziellessen, F. O.,** and **Barnes, A. R.**: Am. Heart J., **6**, 349, 1931. (13.) **Mallory, T. B.**: New England J. Med., **216**, 392, 1937. (14.) **Marvin, H. M.,** and **Sullivan, A. G.**: Am. Heart J., **10**, 705, 1935. (15.) **Mönckeberg, J. G.**: Virch. Arch. f. pathol. Anat. u. Physiol. u. f. Klin. Med., **172**, 472, 1904. (16.) **Sosman, M. C.,** and **Wosika, P. H.**: Am. J. Roent., **30**, 328, 1933. (17.) **White, P. D.**: Heart Disease, New York, The Macmillan Company, 2d ed., p. 232, 1937. (18.) **Willius, F. A.,** and **Camp, J. D.**: Med. Clin. of North America, **19**, 497, 1935.

VARIETIES OF SINGLE CORONARY ARTERY IN MAN, OCCURRING AS ISOLATED CARDIAC ANOMALIES.

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Congenital absence of one or other coronary artery appears to be a very rare anomaly in man. Especially is this so when it satisfies Hyrtl's postulate that one artery really supplies the whole heart, and the anomaly is not merely a matter of a common aortic orifice of the two arteries or an unusual origin of one of the other artery (*i. e.*, a misplaced anlage). Slightly misplaced or accessory coronary orifices are not uncommon (see Richter[14]). One of us[9] has already reported a case where, associated with idiopathic cardiac hypertrophy (von Gierke's disease?), the left coronary artery arose from the pulmonary artery without noticeable damage to the left ventricle. The variability of coronary artery distribution is well shown in the article by Ehrich, de la Chapelle and Cohn.[4]

We wish to record 2 cases of congenital absence of a coronary artery, both incidental findings at autopsy, in one of which the left

coronary artery and its branches supply the whole heart, while in the other a large right coronary early in its course gives off a branch which passes behind the aorta, past the usual site of origin of a left coronary, and is distributed to part of the left ventricle. As study of the literature indicates that these 2 cases are characteristic of the two chief varieties of absence of a coronary artery in man, a classification has been attempted.

CASE 1.—(P. G. H. Aut. 34,791.) A small, obese woman, aged 44, died of a pulmonary embolism. Previous to her last illness there were no signs of cardiac weakness observed. No history of cardiac anomalies in the family was elicited. *Autopsy* (Dr. W. E. Ehrich), in addition to the pulmonary embolism, revealed an enlarged heart (400 gm.) and a chronically thickened mitral valve.

*Coronary Artery System.** The right coronary artery is completely absent. There is no sign of an orifice in the pulmonary or high in the aorta or in the right anterior sinus of Valsalva. A large left coronary, showing a moderate degree of sclerosis, arises from its normal site in the left sinus of Valsalva. Its circumflex portion follows a normal course in the coronary sulcus, but continues all the way around the right ventricle to a point within 1.5 cm. of the aorta, where it divides into small terminal branches. It gives off the normal anterior descending branch and one in the posterior interventricular septum, similar to that normally arising in this position from the right coronary. The anterior descending can be opened to the very apex where it is lost in fat (*i. e.*, somewhat further than normal) (Fig. 1). No abnormal branches are found. Sections from the right ventricle show normal musculature, with no signs of degenerative or inflammatory change. There is some penetration of pericardial fat between the myocardial bundles.

CASE 2.—(P. G. H. Aut. 35,147.) An emaciated negress, aged 35, died of carcinoma of the uterus with widespread metastases. There were no clinical indications of a deficient circulation and no history of cardiac anomaly in the family was obtained. *Autopsy* (Dr. W. E. Ehrich), in addition to the carcinomatosis, revealed absence of the left coronary artery, otherwise a normal heart (285 gm.), a practically normal aorta, and thrombosis of the left iliac vein.

Coronary Artery System. A very large right coronary artery (1 cm. in circumference) arises from the right anterior sinus of Valsalva and no vestige of a left coronary artery can be found. As the right coronary is traced, it is found to give off—2 cm. from its origin—a branch (4 to 5 mm. in circumference) which courses posterior to the aorta and between it and the left auricular appendage. It can be traced to the base of the left ventricle, where it gives off branches that supply a major part of the left ventricle (and presumably, the left auricle). The right coronary artery also gives off a moderate-sized branch, 2 mm. from its orifice, which disappears into the septum, but does not reappear, as in Bochdalek's and Sanes' cases (to be mentioned later). These branches thus constitute a partial substitute for the missing left coronary. The main artery follows its normal course in the *A–V* groove, giving off several large branches (Fig. 1), and ending in several terminal twigs on the posterior surface of

* As both hearts here described were opened routinely, the anomalies being unexpected findings of the postmortem examination, injection preparations were not feasible. The anomalous arrangement and distribution, however, could be readily made out in each case by exploration with forceps and fine scissors.

the left ventricle, shortly after passing the interventricular septum. The branch that most closely corresponds to the posterior descending arises at the right border, passing horizontally across the posterior surface until it reaches a point above the interventricular septum, when it turns and

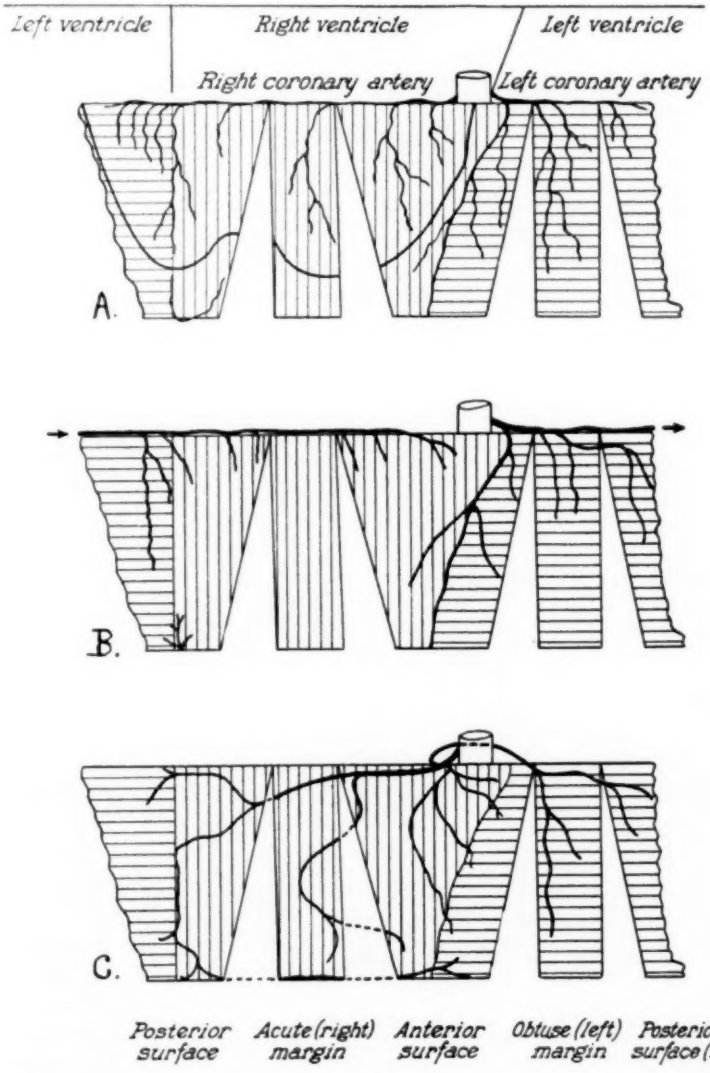


FIG. 1.—*A*, Diagram showing average distribution (after injection with barium-gelatin mixture) of the superficial coronary arterial system (from Ehrich, de la Chapelle and Cohn). *B*, Distribution of left coronary and branches in Case 1 (absent right coronary artery). *C*, Distribution in Case 2 of right coronary and branches (absent left coronary artery). Note: The large septal branch arising close to the aortic orifice has not been drawn, as these diagrams represent the superficial only.

courses along the septum at least as far as the apex. Sections from various parts of the heart, including the base of the left ventricle, show some increase of fine periarterial fibrosis, equally throughout the heart.

Comment. These cases have been assembled with those found in the literature into three tables: Table 1, cases of absent right coronary artery, all of which comply with Hyrtl's concept; Table 2, cases of absent left coronary artery, where the left heart is supplied by one or two apparent branches of the right coronary; Table 3, miscellaneous unclassified cases. Our Case 1 appears to satisfy Hyrtl's postulate that one artery should supply the whole heart,

TABLE 1.—CASES OF ABSENCE OF RIGHT CORONARY ARTERY.*

Remaining artery supplies both sides of heart, with normal or almost normal distribution of branches (Hyrtl type).

Author.	Missing cor.	Age, (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. of heart (gm.).
Plaut (1922)	R.	37	M.	L. (left) cor. traverses entire cor. sulcus with a normal ant. desc. and large branches arising at R. (right) and L. borders of heart; a large branch from ant. desc. crosses R. V. to heart border; R. cor. is represented by small brownish dimple in aorta that is without functional significance	Endocarditis lenta.	
Petren (1930)	R.	33	M.	Half way down ant. surf. of heart, ant. desc. curves around R. V. and upward to post. furrow; L. circumflex continues well beyond post. furrow to within 1 cm. of aorta, giving branches to both vents. and ends in 2 small branches to R. A. and R. V.	Apoplexy	520
Kockel (1934–1935)	R.	39	F.	L. circumflex continues around to ant. surf. of R. V. with various branches to R. A. and R. V., as well as customary L. cor. branches	Pneumonia.	
Richter (Case 1) (1937)	R.	63	M.	L. cor. arises 2 cm. above sinus; its circumflex continues around R. V. to conus pul. with appropriate branches	Ca. of stomach, etc.	150
Krumbhaar and Ehrich (Case 1)	R.	44	F.	The circumflex branch of L. cor. continues around R. V. to within 1.5 cm. of the aorta; its branches correspond to those normally given off by both R. and L. arteries; no anomalous branches found	Chr. valvular disease; pulmonary embolism.	400

* In none of the cases listed in this and the succeeding table was myocardial weakness attributed to the anomalous arterial supply. Early reported cases, such as Thebesius' (1716), Otto's (1830), Hyrtl's (1841), are regarded as too indefinite to be tabulated.

without conspicuous anomalous branches. Here there is no question of a misplaced anlage, or of an anomalous vessel that might be regarded as an abortive right artery. The large branches that normally come from the right here arise from the left coronary. Thus it falls in the same group as Petren's,[12] Kockel's,[8] Richter's first case and Plaut's[13] (though here a small dimple apparently represented the anlage of the missing vessel). It is perhaps not a coincidence that in all of these cases it was the right coronary artery that was missing, though we know of no explanation for such a correlation.

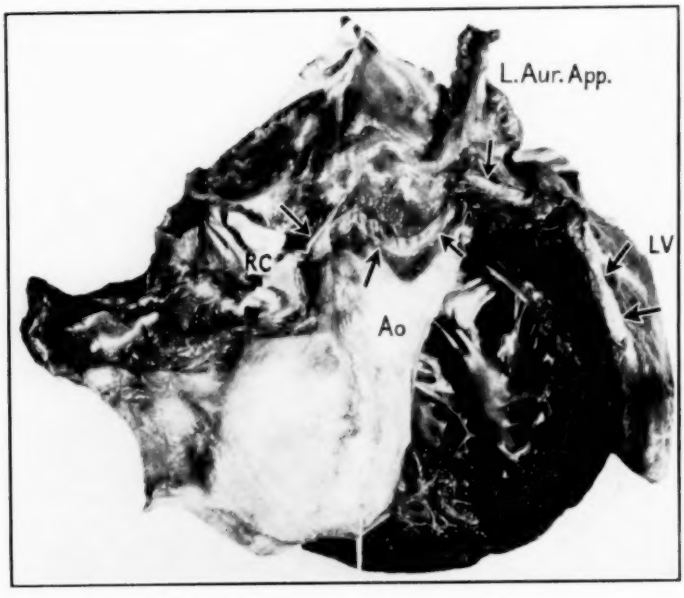
The nature of the compensatory arrangement of the cases in Table 2 is debatable. In our Case 2, for example, although the

A

B

FIG. 2.—Case 1. *A*, Showing a large single orifice in the left sinus of Valsalva. *B*, A superoposterior view of the heart showing the opened single left coronary artery as still a large vessel on the posterior surface of the right ventricle.

A



B

FIG. 3.—Case 2. *A*, Showing a large single orifice in the right sinus of Valsalva (when the heart was opened in this case, the septal cut was made further to the right on the anterior wall than in Case 1). *B*, A superior view of the heart showing the opened anomalous branch (marked with arrows) arising from the right coronary, passing between the aorta and left auricular appendage to be distributed to the upper left ventricle.

anomalous branch that fed the basal part of the left ventricle, arose well down the right coronary and thus several centimeters from the normal site of origin of the left coronary, it eventually followed the course of a hypoplastic left coronary and *might* be regarded as a left coronary, arising from a badly misplaced anlage. To the writers it seems more probable that Case 2, like the others

TABLE 2.—CASES OF ABSENCE OF LEFT CORONARY ARTERY.*

The left side of the heart is supplied by 1 or 2 large, more or less abnormal, vessels that appear to be hypertrophied branches of the right coronary but suggest the possibility of misplaced anlage of origin.

Author.	Missing cor.	Age (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. of heart (gm.).
GROUP 1.—*Substitution by 2 Branches of Right Coronary: a Septal Branch, and One Passing Behind Aorta.*						
Bochdalek (1867)	L.	60	F.	R. cor. divides in 3 branches, the first of which follows normal course of R. cor.; the second, passing behind aorta, substitutes for L. cor; the third passes between aorta and pul. art. through sept., substituting for ant. desc.	Chr. mitral and aortic endocarditis	
Sanes (1937)	L.	3	M.	Large art. arising in R. sinus (a dimple adjacent) shortly divides into 3 branches: 1, an enlarged R.; 2, an anomalous L., passing between A. and L. A. to cor. sulcus, corresponding to a L. circumflex; 3, a branch sinking into the sept. between A. and pul. art. to appear on ant. surf. like ant. desc.	Acute glomerulonephritis	
Krumbhaar and Ehrich (Case 2)	L.	35	F.	Arising from large R. cor. (2 cm. from aorta), a large anomalous branch (4 to 5 mm. in diam.) passes behind aorta and between it and L. auric. appendage to feed upper half of L. V.; another large branch passes between aorta and pul. art. to V. sept.; the main art. continues in *A-V* groove past intervent. sept. post. where it ends in several small branches; it furnishes both ant. and post. desc. branches	Carcinomatosis	285
GROUP 2.—*Substitution by Septal Branch Only.*						
Gallavardin and Ravault (1925)	L.	45	F.	R. cor. divides almost at orifice into 2 equal branches, 1 acting as R., the other as L. cor., with circumflex and ant. desc. branches; the left branch, however, passes between aorta and pul. art.	Chr. mitral and aortic endocarditis	
Born (1933) (1 case)	L.	54	M.	Approx. nor. R. cor. goes in cor. sulcus to L. border of heart; large branch, starting near aortic orifice, goes between aorta and pul. art. into vent. sept. to reach ant. sulcus where it divides into an ant. desc. and a circumflex branch	...	750
Kintner (1931)	L.	65	M.	From a single orifice in R. sinus a large R. cor. pursues a normal course; an anomalous branch passes between aorta and pul. art. down and to L. reaching sept., where it curves ant. and just before reaching the surf. gives off branches corresponding to ant. desc. and L. circumflex	Pneumonia and renal insufficiency	

* The question as to whether these cases represent true absence of an artery or misplaced anlage is discussed in the text.

in Table 2, represents a true absence of the left coronary and that the substitute was a true branch of the right coronary, hypertrophied to meet the demand caused by the absent left coronary. Especially does this seem probable in the 3 cases of this group in which two separate branches of the right coronary substitute for the missing vessel. In any case, however, it is clear that none of the hearts in Tables 2 and 3 satisfies Hyrtl's postulate. For various reasons, these cases are difficult to evaluate. For instance, we have no definite way

of deciding whether a given anomalous vessel merely arises from a misplaced origin, or whether it is a branch developed to take the place of the missing vessel and distributed more or less in the same way. The dimple adjacent to the single coronary orifice in Sanes' case suggests that this, as in Plaut's case, represents a missing anlage and that the entire coronary system in these cases has arisen from one anlage. This phase of the subject need not be further elaborated here.

TABLE 3.—MISCELLANEOUS UNCLASSIFIED CASES OF ABSENT CORONARY ARTERY.

Author.	Missing cor.	Age (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. o heart (gm.).
Engelmann (1898)	R.	..	..	Large L. circumflex passes far onto post. surf. of R. V.; 1 cm. below beginning of normal ant. desc. a very large anomalous vessel passes obliquely over lower half of R. V. to divide in terminal branches on post. surf. of R. V.; a small vessel arises from L. cor. to pass between aorta and pul. art. to a point behind R. auric. appendage supplying post. R. V.	...	
Smith and Graber (1926)	L.	46	M.	The only cor. arising from aorta follows normal course of R. cor. to post. vent. sept.; here it divides into a larger desc. branch and a smaller branch which continued in *A–V* groove; post. desc. branch after reaching apex passed upward along ant. intervent. groove to anast. with a branch from first portion of main art.; the combination anastomosing also with a branch from post. desc.*	Coronary obstruction	930
Richter (Case 2) (1937)	R.	Adult	..	L. cor. divides into 3 branches: 1, ant. desc. which continues 5 cm. past the apex on post. wall; 2, a small L. circumflex, finishing behind L. auric. appendage; 3, a large branch, that goes over conus pul. to cor. furrow of R. V.; two of its branches supply post. surf. of R. and L. Vs.	...	370

* The anomalous arterial supply of the left ventricle in this case is apparently unique in the literature. Description is not sufficiently detailed to carry intrinsic proof of what appears to be an improbable explanation.

The cases of Bochdalek[1] and Sanes[15] comes closest to our second case, in that both, having but one coronary orifice, present anomalous branches of the right coronary, one of which passes behind the aorta and then between it and the left auricle to the left ventricle; while another passes into the ventricular septum. In these cases, however, the septal branch was more important than in our case, reappearing after its passage through the septum on the surface of the ventricle, which ours did not.

In the cases of Born,[2] Kintner,[7] and Gallavardin and Ravault,[5] on the other hand, substitution is accomplished by one anomalous branch of the right coronary, which, either sinking into the septum (Born) or passing between aorta and pulmonary artery (the other 2), appears on the anterior surface to give rise to a left circumflex and an anterior descending artery. As to the question whether these cases should be regarded as examples of anomalous origin of the left coronary or of its true absence, the division of the main artery into right and left branches almost at the aorta would favor the former view; the markedly anomalous and differing courses, the latter view. Though Kintner and Sanes regarded their cases as representing an

anomalous left coronary, there was but one orifice and the distribution was anomalous. The descriptions clearly place both in our Table 2.

The cases of Engelmann,[3] Smith and Graber,[17] and Richter[14] (Case 2) have been assembled in a miscellaneous group that resists classification. Such cases as those of Kugel,[10] de Vries,[18] Shapiro,[16] Mönckeberg[11] and Walcher[19] are not considered here, both because of inadequate description in some cases and because they all were associated with other grave cardiac anomalies. No other clear cases of absent coronary artery have been found by us in the literature.

The pathogenesis of these anomalies cannot yet be explained. Some authors have attributed the absence of one of the arteries to lack of the appropriate anlage, as the Plaut and Sanes dimples would suggest; others (with less probability) to closure of the vessel in question in fetal life. The possibility of the anomaly being due to a misplaced origin of one of the coronaries in some of the cases has already been mentioned.

Summary. 1. Two cases of absence of a coronary artery are reported, both incidental findings at autopsy, and apparently causing no damage to the myocardium.

2. In the first case, a large left coronary continued around the *A–V* groove, to the anterior surface of the right ventricle, giving off branches that corresponded to those normally given off by both arteries (Hyrtl type of absent coronary).

3. In the second case, a large right coronary artery supplied most of the heart with conventional branches. Near its origin, however, it gave off one large anomalous branch which passed behind the aorta to supply a good part of the left ventricle and another to the ventricular septum. The possibility must be considered that the former of these represents a true left coronary arising from a misplaced anlage, though the similar cases of Bochdalek and Sanes makes this very unlikely.

4. Other cases of absence of a coronary artery, or possibly misplaced anlage of origin, are tabulated, all but 3 of which fall into two groups corresponding to the types of the 2 cases reported here.

REFERENCES.

(1.) **Bochdalek, J.**: Virch. Arch., **41**, 260, 1867. (2.) **Born, E.**: Ibid., **290**, 688, 1933. (3.) **Engelmann, G.**: Anat. Anz., **14**, 348, 1898. (4.) **Ehrich, W., de la Chapelle, C. E.,** and **Cohn, A. E.**: Am. J. Anat., **49**, 241, 1931. (5.) **Gallavardin, L.,** and **Ravault, P.**: Lyon Med., **136**, 270, 1920. (6.) **Grätzer, G.**: Virch. Arch., **262**, 608, 1926. (7.) **Kintner, A. R.**: Arch. Path., **12**, 586, 1931. (8.) **Kockel, H.**: Ziegl. Beitr., **94**, 220, 1934–35. (9.) **Krumbhaar, E. B.**: Bull. Internat. Assn. Med. Mus., **10**, 108, 1924. (10.) **Kugel, M. A.**: Am. Heart J., **7**, 263, 1931–32. (11.) **Mönckeberg, J. G.**: *In* Henke and Lubarsch's Handb. d. spez. path. Anat. u. Hist., Berlin, Julius Springer, **2**, 83, 1924. (12.) **Petren, T.**: Virch. Arch., **278**, 158, 1930. (13.) **Plaut, A.**: Frankf. Ztschr. f. Path., **27**, 84, 1922. (14.) **Richter, O.**: Virch. Arch., **299**, 637, 1937 (with literature). (15.) **Sanes, S.**: Am. Heart J., **14**, 219 1937 (with literature). (16.) **Shapiro, P. F.**: Arch. Path., **10**, 671, 1930. (17.) **Smith, F. M.,** and **Graber, V. C.**: Arch. Int. Med., **38**, 222, 1926. (18.) **deVries, W. M.**: Beitr. z. path. Anat. u. allg. Path., **64**, 39, 1918. (19.) **Walcher, K.**: Virch. Arch., **234**, 73, 1921.

THE ANEMIA OF ALCOHOL ADDICTS.

OBSERVATIONS AS TO THE RÔLE OF LIVER DISEASE, ACHLORHYDRIA, NUTRITIONAL FACTORS AND ALCOHOL ON ITS PRODUCTION.

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RECENT studies from this clinic on the polyneuritis of the alcohol addict[3, 8–10] have made us aware of the frequent occurrence of macrocytosis and macrocytic anemia in these patients. Spies and Chinn,[12] in a study of pellagrins, most of whom were alcohol addicts, found quantitative anemia in about two-thirds of their subjects. In 75% of these, the anemia was of the macrocytic hyperchromic variety. Several observers have called attention to the frequent occurrence of macrocytic anemia in subjects having cirrhosis of the liver; Wintrobe[15b] reported the incidence to be about 40% in 44 subjects, while Rosenberg and Walters[11] reported macrocytosis in about 90% of their 48 patients, 31 of whom were known alcohol addicts. Macrocytic anemia, therefore, is frequently observed in 3 syndromes common in alcohol addicts: polyneuritis, pellagra and liver cirrhosis. As data are not available concerning quantitative measurements of the red blood cells in alcohol addicts, we are unable to determine whether the high incidence of macrocytosis is characteristic only of polyneuritis, pellagra and liver cirrhosis, or possibly of an underlying liver disease, or of alcohol addiction itself; or whether some other factor plays the decisive rôle. To decide this point, if possible, is the purpose of the present study.

The subjects in this study are 159 alcohol addicts admitted to the wards of the Psychiatric Division of Bellevue Hospital who presented evidence of polyneuritis (139), pellagra (40), "alcoholic" encephalopathy[1] (24), liver cirrhosis (30), and "alcoholic" stomatitis[2] (48), and were therefore transferred to the division's medical service. Many of the subjects presented two or more of these syndromes simultaneously. This group of 159 patients is hereafter, for convenience, referred to as the "complicated" group. Patients having surgical complications, acute infections, syphilis, or tuberculosis, are not included in this group. An additional group of 25 alcohol addicts who showed none of the above clinical pictures or other stigmata of alcohol addiction were selected for control observa-

tions. Each subject in this group had had two or more previous admissions within a year to the alcoholic wards. This latter group is hereafter, for convenience, referred to as the "uncomplicated" group.

During the first 3 to 5 days of hospitalization, while the blood studies and routine observations were carried out, all the patients received our ward basal diet.[8] Following these observations, therapy was instituted. This report, however, deals only with the blood status as found during the preliminary period of observation.

Methods. In the first 61 subjects, Haden's[4] constants, corrected for our laboratory, were determined. The corrected values were obtained by determinations in 20 apparently normal subjects. In the remaining 123 subjects Wintrobe's[15a] methods were followed. In order to tabulate and average the size of the red cells, the maximum normal size of each method is designated as 100%. The size of the red blood cells is therefore reported in per cent of the maximum normal size.

Arbitrarily we have chosen the following values as normal:
Red blood cells: 5,000,000 = 100%.
Hemoglobin: 14.5 gm. per 100 cc. = 100%.
Color index: 0.85 to 1.15.
Volume index: 0.85 to 1.15 (1.15 = 100%).
Mean corpuscular volume: 75 to 95 cu. μ (95 cu. μ = 100%).

The anemia found is classified according to size and color index of the red cells. Following Wintrobe's[15a] criteria and classification, our subjects showing anemia are divided into four groups: macrocytic, normocytic, simple microcytic, and microcytic hypochromic anemia.

Gastric analyses and liver function studies were performed by methods described in previous publications from this clinic.[6,7]

TABLE 1.—QUANTITATIVE DATA ON THE RED BLOOD CELLS OF 184 ALCOHOL ADDICTS.

Group.	No. of subjects.	RBC in millions.			Hgb. in grams.			Color index.			Size of RBC in % of max. normal.		
		Mean.	Variation.		Mean.	Variation.		Mean.	Variation.		Mean.	Variation.	
			Min.	Max.		Min.	Max.		Min.	Max.		Min.	Max.
Uncomplicated	25	4.81	4.19	5.48	13.5	11.1	15.4	0.98	0.91	1.15	102	68	120
Complicated	159	3.80	1.64	5.95	12.1	4.7	18.2	1.11	0.70	1.48	101	61	175
No anemia	62	4.58	4.00	5.95	13.9	8.6	18.2	1.04	0.72	1.37	101	80	120
Anemia	97	3.19	1.64	3.97	10.5	4.7	14.6	1.15	0.70	1.48	101	61	175

Results. We have arbitrarily designated subjects having 4 million or more red cells as not anemic, and all subjects having less than this number as having anemia. On this basis none of the "uncomplicated" subjects, and 61% of the "complicated" subjects show anemia. In Table 1 we have tabulated in the two major

groups the average, as well as the minimum and maximum, red blood cell count, grams of hemoglobin, color index, and size of the red cells; the "complicated" group was further subdivided into those with and without anemia. The average size of the red cells in the two major groups is practically identical, corresponding to about 96 cu. μ; the color index in the "complicated" group, however, averaged 1.11, which is significantly greater than the average of 0.98 in the "uncomplicated" group, and represents definite hyperchromia. In Table 2 we have classified the red cells as simple microcytic, hypochromic microcytic, normocytic, and macrocytic in type. The incidence of macrocytosis in both the "uncomplicated" and "complicated" group was about 50%. When, however, the "complicated" group is divided into those with and without anemia, the incidence of macrocytosis is higher in the anemic group. Further examination of the anemic group reveals that the incidence and the degree of macrocytosis, as well as the degree of hyperchromia, vary directly with the degree of anemia. The incidence of macrocytosis in the "complicated" group without anemia is, however, somewhat lower than in the "uncomplicated" group, apparently due to a higher incidence of simple microcytosis in the former group.

TABLE 2.—INCIDENCE OF THE VARIOUS TYPES OF RED BLOOD CELLS IN 184 ALCOHOL ADDICTS.

Group.	No. of subjects	Hypochromic microcytic.		Simple microcytic.		Normocytic.		Macrocytic.	
		No.	%.	No.	%.	No.	%.	No.	%.
Uncomplicated	25	0	...	2	8.0	11	44.0	12	48.0
Complicated	159	2	1.3	12	7.5	60	37.7	85	53.4
No anemia	62	1	1.6	10	16.1	29	46.7	22	35.4
Anemia	97	1	1.0	2	2.0	31	32.0	63	65.0

TABLE 3.—DATA ON THE "COMPLICATED" GROUP OF ALCOHOL ADDICTS.

Group.	No. of subjects.	Anemic, %.	Mean of:		Per cent.			
			Color index.	Size R.B.C.	Hypochromic microcytic.	Simple microcytic.	Normocytic.	Macrocytic.
Polyneuritis	69	52.1	1.15	100.6	...	8.6	40.5	50.7
Stomatitis	48	75.0	1.15	102.1	...	4.1	35.4	60.4
Pellagra	40	65.0	1.11	96.5	2.5	5.0	42.5	50.0
Cirrhosis	30	70.0	1.10	99.0	3.3	16.5	26.4	52.8
Encephalopathy	24	58.3	1.06	102.2	...	8.3	29.1	62.5
Total patients	159	61.0	1.11	101.0	1.3	7.5	37.7	53.4

In Table 3 the "complicated" group is divided into the various listed diseases.* In each disease we have tabulated the frequency of anemia, mean color index, mean size of the erythrocytes, and the incidence of the various types of erythrocytes classified as to size.

* As 85% of the "complicated" group had polyneuritis, we include in the polyneuritic group only subjects having polyneuritis without other stated complications. In the other sub-groups listed in Table 3, subjects are included irrespective of the presence or absence of another listed disease.

The incidence of quantitative anemia in the listed diseases varies from 52.1% in the subjects having only polyneuritis to 75% in the subjects having stomatitis. The average size of the red cells in the whole "complicated" group is slightly greater than normal, corresponding to 96 or 97 cu. μ. This is also true for the various sub-groups except the pellagrins and cirrhotics whose red cells average slightly below the upper limits of normal, corresponding to 92 and 94 cu. μ., respectively. The averages of the color indices in all five sub-groups show hyperchromia. The incidence of macrocytosis varies from 50% in the pellagrins to 62.5% in the "encephalopaths." The combined incidence of normocytosis and macrocytosis is greater than 90% in all groups except in that having cirrhosis, where this figure totals 79.2%. It is in this cirrhotic group that microcytosis was most frequently present, occurring apparently at the expense of normocytosis; this finding we ascribe to the higher incidence of gastro-intestinal bleeding in this group.

Achlorhydria was found but once in the 25 "uncomplicated" subjects. In the "complicated" group achlorhydria was present in 48.7% of the 119 subjects tested. Joffe and Jolliffe[6] reported in detail on 105 of these subjects in their study of gastric acidity in alcohol addicts. The additional 14 subjects in no way alter the findings in that study. There is no apparent relationship between achlorhydria and macrocytosis in these "complicated" alcohol addicts, as macrocytosis occurred in 43% of those having achlorhydria and in 52% of those having free acid. There was also no apparent relationship between the degree of anemia and achlorhydria, as those having achlorhydria had an average erythrocyte count of 3,830,000, while those having free acid had an average count of 3,600,000 red cells.

In this study, we have arbitrarily selected the degree of bromsulphalein retention at the end of 30 minutes as an index of liver dysfunction. None of the subjects in the "uncomplicated" group showed a retention of the dye as great as 25%; average 9%. In the "complicated" group 48 of the 99 subjects tested showed a dye retention of 25% or more; average 30%. Macrocytosis occurred in 52% of the group showing a dye retention of 25% or more, as compared with a 58% incidence of macrocytosis in those having a dye retention of less than 25%.

In this study, our criteria for the diagnosis of cirrhosis of the liver require that the ascites cannot be explained on another basis and that visible lateral abdominal veins be present. Our cirrhotic group thus includes only those having liver failure. We have, therefore, considered separately those subjects having and not having an enlarged liver. In the "complicated" group 54% had an enlarged liver, 47.1% of whom had macrocytosis; however, 61% of the "complicated" group whose liver was not enlarged also showed macrocytosis.

In the blood smear examination the outstanding finding was the lack of unusual qualitative changes, except occasionally in subjects having a considerable anemia. The red cells as a rule were of uniform size, and if no quantitative measurements had been done one would not as a rule have called the cells macrocytic. There was a notable lack of anisocytosis, and evidence of regenerative changes was rare. The cells did appear in most instances to be well filled with hemoglobin.

Discussion. It has been shown in this study that anemia is not likely to be found in "uncomplicated" alcohol addicts, but was present in 61% of 159 alcohol addicts having the various named diseases. Macrocytosis of some degree, however, occurred in 48% of the "uncomplicated" group, an incidence only slightly less than the 53% found in the "complicated" group. In two diseases common in alcohol addicts, namely, cirrhosis of the liver and pellagra* (in the alcohol addict), macrocytosis has been frequently reported. In the subjects having liver cirrhosis Wintrobe[15b] attributed the anemia to the inability of the liver to store the necessary hematopoietic principle. While Wintrobe did not state the incidence of alcoholism in his cirrhotic patients, about 65% of those reported by Rosenberg and Walters[11] were known alcohol addicts. That our figures are not peculiar to our laboratory or our group of patients is evident from the fact that in our pellagrins the incidence of anemia and macrocytosis, and the degree of hyperchromia, is practically identical with that reported by Spies and Chinn.[12] The incidence of 53% of macrocytosis in our subjects with liver cirrhosis is lower than that reported by Rosenberg and Walters,[11] and higher than the incidence reported by Wintrobe.[15b] Our figures, therefore, confirm the high incidence of macrocytosis in alcohol addicts having pellagra or liver cirrhosis.

We hesitate, however, to attribute the macrocytosis or macrocytic anemia of our alcohol addicts, either in those having or not having liver cirrhosis, to inability of the liver to store the necessary hematopoietic principle. Our reasons for this belief include the following: 1, Wintrobe's[15b] observation that mild or moderate cirrhosis is not accompanied by macrocytic anemia. 2, The incidence of macrocytosis is no higher in patients having clinical cirrhosis than in those having the other named diseases, or even very much higher than in alcohol addicts without recognized somatic stigmata of alcoholism. 3, The incidence of macrocytosis is no higher in patients having the greater degree of liver dysfunction than in those having the lesser degree, and is no higher in those having enlarged livers than in those whose livers were not enlarged.

That the hyperchromic macrocytic anemia of alcohol addicts is not due to marked reduction or absence of an intrinsic factor as in

* In endemic Southern pellagra most observers[5,14] report the anemia, when present, as microcytic.

Addisonian pernicious anemia seems definite. The reasons for this belief include the following: 1, Liver extract or gastric mucosa is not necessary as a rule to produce a remission. In our cases a good diet without liver or kidney, plus vegex,* brewers' yeast* or liver residue lacking the antipernicious anemia factor† in most subjects relieves the anemia within a short time. 2, The anemia is associated, more often than not, with free acid in the gastric contents. 3, Spies and Payne[13] have reported that the gastric juice of alcohol addicts having pellagra will produce a reticulocyte response in patients in a relapse of pernicious anemia.

We are not prepared to state definitely the cause of the macrocytosis in these subjects, even though alcohol addiction is a factor common to all subjects studied. That it is due to alcohol *per se* seems to us to be untenable in view of the fact that such diseases as pellagra, polyneuritis and cirrhosis of the liver occurring in alcohol addicts are now quite generally believed to be due not to the direct action of alcohol but to associated factors. A history of an irregular or more often of a definitely inadequate diet over varying periods of time was almost a constant finding in our hospitalized subjects. We are therefore inclined to relate the macrocytosis to an extrinsic deficiency of some necessary hematopoietic principle required to maintain normocytosis.

Summary and Conclusions. A quantitative study of the red blood cells in 184 cases of alcohol addiction is reported. Of these subjects, 159 were "complicated" in that they had, in addition to alcohol addiction, one or more of the following diseases: polyneuritis, pellagra, "alcoholic" stomatitis, "alcoholic" encephalopathy, or liver cirrhosis; 25 of these subjects were "uncomplicated" in that they had none of the above listed diseases or other recognized stigmata of chronic alcoholism.

In our subjects, quantitative anemia did not occur in the "uncomplicated" group, but was present in 61% of the "complicated" group. However, macrocytosis was present in about 50% of both groups. Macrocytic anemia in these alcohol addicts was not limited to subjects manifesting pellagra or cirrhosis of the liver, but occurred as well, and in about the same frequency, in subjects having polyneuritis, "alcoholic" stomatitis, and "alcoholic" encephalopathy. There was also no correlation between the frequency of macrocytosis and achlorhydria, severity of liver damage, or the presence of an enlarged liver. In view of these findings we are inclined to regard the macrocytosis of the alcohol addict not as a manifestation of inability on the part of the liver to store a hematopoietic principle but as an extrinsic deficiency of some necessary hematopoietic substance required to maintain normocytosis.

* Courtesy of Vegex, Inc., New York.
† Courtesy of Lederle Laboratories, Inc., New York.

REFERENCES.

(1.) **Bender, L.**, and **Schilder, P.**: Arch. Neurol. and Psychiat., **29**, 990, 1933. (2.) **Blankenhorn, M. A.**, and **Spies, T. D.**: J. Am. Med. Assn., **107**, 641, 1936. (3.) **Goodhart, R.**, and **Jolliffe, N.**: Ibid., **110**, 414, 1938. (4.) **Haden, R. L.**: J. Lab. and Clin. Med., **15**, 736, 1930. (5.) **Huck, J. G.**: Bull. Johns Hopkins Hosp., **34**, 157, 1923. (6.) **Joffe, P. M.**, and **Jolliffe, N.**: Am. J. Med. Sci., **193**, 501, 1937. (7.) **Jolliffe, N.**: Ibid., **186**, 640, 1933. (8.) **Jolliffe, N.**, and **Colbert, C. N.**: J. Am. Med. Assn., **107**, 642, 1936. (9.) **Jolliffe, N.**, and **Joffe, P. M.**: Proc. Soc. Exp. Biol. and Med., **32**, 1161, 1935. (10.) **Jolliffe, N., Colbert, C. N.**, and **Joffe, P. M.**: Am. J. Med. Sci., **191**, 515, 1936. (11.) **Rosenberg, D. H.**, and **Walters, A.**: Ibid., **192**, 86, 1936. (12.) **Spies, T. D.**, and **Chinn, A. B.**: J. Clin. Invest., **14**, 941, 1935. (13.) **Spies, T. D.**, and **Payne, W. A.**: Ibid., **12**, 229, 1933. (14.) **Turner, R. H.**, and **Shelton, E.**: Am. J. Med. Sci., **185**, 381, 1933. (15.) **Wintrobe, M. M.**: (*a*) Am. J. Clin. Path., **1**, 147, 1931; (*b*) Arch. Int. Med., **57**, 289, 1936.

CONVULSIVE (PENTAMETHYLENETETRAZOL) SHOCK THERAPY IN DEPRESSIVE PSYCHOSES.

Preliminary Report of Results Obtained in Ten Cases.*

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Results obtained by convulsive shock therapy in schizophrenic psychoses have been so impressive that I decided to try a modified treatment upon a case of depressive psychosis. Encouraged by excellent and immediate response, I treated 9 other cases with very favorable results. Since, hitherto, methods of shock therapy successful with schizophrenia have not succeeded with the depressive psychoses, and since almost no similar reports appear in the literature, the 10 cases which are the basis of this preliminary report should be of interest.

Meduna[5] first used convulsive shock therapy in schizophrenia. Acting upon the observation that convulsive states and the schizophrenic process were apparently biologically incompatible, he perfected a method of inducing convulsions by means of a camphor-like preparation, pentamethylenetetrazol. He has reported results obtained in 74 chronic schizophrenic patients with a disease of 2 to 3 years' duration: 39% were cured; 15% improved; and 46% were unchanged.

Ellery[2] after a personal visit to Meduna's clinic quotes results in 110 schizophrenic patients: 80% of early cases obtained good remissions, but patients ill longer than 4 years failed to obtain any good results. Friedman[4] recently quoted Meduna's 110 cases: 96% of cases treated during the first year of the disease were improved

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(this is a 16% increase over Ellery); while less than 8% of cases of 3 or more years' duration showed improvement.

These results are distinctly encouraging and at least equal to the best results reported from insulin shock therapy in early cases. It may be that convulsive shock therapy, because of its simplicity and apparent relative safety, may replace insulin shock therapy. Personally, I still prefer insulin shock therapy in undernourished, acutely excited and paranoidal types of schizophrenia; but am using pentamethylenetetrazol for the well nourished, catatonic, hebephrenic and depressed types.

Because of the encouraging results obtained from insulin shock therapy in schizophrenia, attempts were made to relieve depressive psychotic patients, with discouraging results.[1] Furthermore, in all previously tried chemical, endocrine or shock therapy methods such as hematoporphyrin, estrogenic, testicular or pituitary hormones, fever therapy and narcosis, no consistent effect in shortening the course of depressions has been observed.

It was decided to try the effect of pentamethylenetetrazol shock therapy upon a chronic resistant agitated case of depression. The almost immediate, abrupt termination of this very severe depressive psychosis (Case 1) led to further experimentation. The extraordinary improvement in 10 consecutive patients suffering from various types of depressive psychoses was a unique therapeutic experience to me and forms the basis of this preliminary report. The observations to date with the use of convulsive shock therapy in chronic agitated and stuporous types of characteristic depressed affective disorders lead me to believe that we may now have a potent agent for terminating these distressing mental states.

There is practically nothing in the literature so far upon convulsive shock therapy in depressive psychoses. Schächter[9] noted improvement in 2 cases of hysteria, 4 anxiety states and 3 depressed patients, as well as schizophrenics that he treated with subcutaneous injections of cardiazol (pentamethylenetetrazol). He states that the psychoneurotic patients after use of cardiazol established a better rapport for psychotherapy; he feels that the shock produced a cessation of the anxiety state since his patients were immediately relieved of fear. Schönmehl[10] in using cardiazol as a means of differentiating hysterical convulsions from true epilepsy noted that its use benefited patients suffering from dazed, stuporous or "Dämmerzustand" states.

Montassut and Lemaire[8] treated depressed states with polycamphosulphonates in non-shock doses. They found that many depressive symptoms in milder cases disappeared, but the profound depressives were apparently not improved.

The following report is based entirely upon results obtained by pentamethylenetetrazol shock therapy in cases that were all essentially affective depressive psychoses. None of these patients

showed schizophrenic features; 4 were severe involutional melancholic types and the remainder were manic depressive depressed types. Uniformly excellent results have been obtained in all these cases to date. All patients appeared completely relieved of the depressive features of the psychosis within 2 weeks after treatment was begun. No complications from the treatment occurred in any of these patients, yet 3 were past 60 years of age and 1 past 57.

Method. All patients were given exhaustive general physical and laboratory studies, including electrocardiography, prior to shock therapy. Our method of treatment consists of routine alkalinization throughout the course to facilitate convulsions. Intravenous injections of pentamethylenetetrazol, 3 to 12 cc., were given every 2 or 3 days of an average course of 5 convulsive shocks.

Precautions against possible fracture or dislocations are taken by bandaging the head and jaw before treatment and by loosening bed clothing to avoid entanglement of the limbs. Tongue and lips are protected by several cotton dental rolls bound with bandage, inserted between the teeth at the onset of the convulsion. No preliminary explanation of the treatment was given the patients. An attempt was made to reassure the patient and avoid arousal of undue apprehension. The individual intravenous injections were given as quickly as possible. Occasionally, the patient failed to convulse from the initial injection. If this occurred an immediate second dose larger than the first was given. The depressed patient who failed to go into a convulsion was left in an agitated apprehensive state for the remainder of the day or until the next treatment. We considered this an unfavorable reaction.

Immediately following the convulsion and passing of the stupor, patients were urged to enter into ward activities. As a rule the patient appeared less tense, relaxed and was amnesic for events just preceding the treatment. The delirious reaction seen in the schizophrenic patient after convulsive shock therapy was strikingly absent in this series. At times the patient awakened in a jocular euphoric mood or made remarks such as "I've come to life"; "Where am I, things are all changed, more natural"; "I am younger again," and so on. For the remainder of the day patients became more interested and less agitated. Gradually a return to the abnormal, emotional, tense state occurred in about 24 to 36 hours; but after the second, third or fourth injection, the excess anxiety or depression seemed to disappear. Some patients displayed perfectly normal emotivity at the end of treatment; some had residual mild anxiety states and one reacted to a hypomanic excitement for a time.

The psycho-physiologic reactions of such a drastic shock therapy upon the organisms are not as yet in any way understood. The profound circulatory shakeup may be responsible for altering cerebral functioning. On the other hand, the drug may act directly upon the autonomic centers of the brain. The convulsion is probably a symptomatic expression of the profound biochemical cellular metabolic reaction and not necessarily an essential factor in producing the change in the affective tone. Whether organic changes occur

in the brain from its use no one can tell as yet. It appears that we may be inducing physiologically in these cases something equivalent to the more hazardous and radical prefrontal lobotomy of Moniz[7] and Freeman and Watts.[3] Pentamethylenetetrazol action is similar to that of camphor, stimulating vasomotor and respiratory centers. In excessive dosage convulsions are produced resembling picrotoxin poisoning.

Psychologically, the mechanisms of shock therapy offer an interesting possible explanation. In cases of severe depression such as those here described, the patient develops the delusion that he is chiefly responsible for a great many ills and griefs, even for crimes. In all our cases strong self-condemnatory feelings of guilt were present; in several cases, patients accused themselves of murder, loathsome and wicked acts, responsibility for national, social, and family evils. Several expressed the wish to die, one or two had attempted suicide, Case 9 desired to have a prefrontal lobotomy performed, hoping for a fatal outcome. According to Menninger[6] this conscious wish to die is not entirely genuine, but is a fantasy representing a wish for punishment. The death instinct is never conscious but is manifested indirectly.

This demand of the conscience for punishment was satisfied by the first and subsequent shock treatments. Although the patient received no previous explanation of the shock therapy, he retained unconscious memory of the pain, as shown by requests not to be subjected to later treatments. But having undergone the painful convulsive therapy, he has approached death psychologically, has suffered punishment, has, as it were, proved himself willing to take punishment. His conscience is then freed; and he can allow himself to start life over again free from the compulsive pangs of conscience.

We consider this type of therapy potentially dangerous and not applicable to casual home or general hospital treatment. It should be given only in a well equipped psychiatric department with experienced psychiatric nursing supervision.

The essential facts concerning the patients treated follow:

Case Abstracts. Case 1. Mrs. J. F., aged 45, had been hospitalized 143 days on account of a severe depressive psychosis. Three members of the immediate family had been psychotic and had become permanent State hospital patients. Prior to present illness the patient had an overactive, elated reaction, following a divorce. "Suddenly I felt a pressure in my chest and became depressed. I knew I'd been cursed." She became very agitated, self-condemnatory and expressed suicidal ideas. After admission, the patient became more agitated and paced the halls: "Call the police, I'm a bad woman. I'm cursed—I have to live in eternal torment. I can never rest. I must give myself up—I'm doomed!" For over 2 months the patient did not talk or respond in any way, became careless of excreta, crawled on the floor and frequently attempted suicide. Commitment papers were arranged for State hospitalization and a grave prognosis given.

At this time convulsive therapy was begun. After the first shock the patient was for a short time responsive and stated: "I feel I am coming to

life." After the second shock: "I want to get up and dress." She also ate in the dining room. After the third and last shock she stated: "I feel so good—I don't know what happened, but isn't it wonderful? I can talk, walk and eat. You have performed a miracle. I don't know how you did it, but I'll never forget it."

The patient merged into a hypomanic state for several weeks, then was dismissed from the hospital and has made a good social adjustment.

Case 2. Mr. F. S., aged 57, had been hospitalized 527 days, suffering from apparently an intractable type of involutional melancholia. The patient, a bachelor, had an unusually marked mother-fixation. Following a conflict over a possible marriage, anxiety symptoms developed with a minor colon dysfunction. Rapidly a severe hypochondriacal depression developed, requiring special nursing care. The patient refused food, was spoon and tube fed; usually behaved in an infantile manner, was constantly tense, noisy and tearful and at times careless of excreta. Many somatic delusions were present concerning the eyes, bladder, bowels and genitalia. "I'm going blind. I've lost my manhood, my testicles are gone. My bladder is weak. I have to go to the toilet 25 times a night." At times paranoid trends were marked; often profane and vulgar in speech, he required frequent seclusion.

All attempts, even with special nurses, to interest the patient in activities failed, as did psychotherapeutic approach. A variety of treatment procedures were tried: Symptomatic sedation, packs, hydrotherapy, hematoporphyrin injections, insulin shock therapy (27 shocks), fever therapy (9 treatments), testosterone and antuitrin injections, 3 weeks of continuous narcosis and benzedrine sulphate. All were ineffectual in improving the mental state, but a 40-pound weight gain resulted from insulin therapy.

After about 1½ years of such failure, convulsive shock therapy was begun and improvement followed the first convulsion. The patient dressed himself, was less tense and began to take an interest in his personal appearance. In about 36 hours after the first injection, relapse occurred, but within 16 days after the first injection the patient was going outside the hospital unaccompanied. Six shocks were given at 3-day intervals. The patient became entirely coöperative, took an interest in other patients, became friendly with nurses, and gradually gave up his resistant paranoidal ideas and somatic complaints. Prior to dismissal, he attended to business affairs and made plans to resume his business. He was dismissed with good insight 22 days after the last shock and has resumed full charge of his business.

Case 3. Miss R. F., aged 28, following disappointment in a love affair and fear of pregnancy, rapidly developed a depressive psychosis. The patient's sister had had a very similar psychosis requiring about 9 months' psychiatric treatment. The patient was admitted about 1 week after the onset, because of suicidal attempts. An extremely apprehensive, agitated reaction with self-accusatory delusions was present. She believed she was pregnant, had syphilis, and had killed her family. She stated she was responsible for the Sino-Japanese War. Ideas of reference were prominent: that nurses called her a loathsome character, and were spies; that newspapers publicized her record, and so on. Close observation was required because of frequent attempts at self-harm. Much sedative and pack therapy was necessary to control agitation.

Insulin shock therapy with 6 hypoglycemic shocks was given at first, without apparent benefit. Convulsive shock therapy was begun 38 days after her admission. Six reactions at 3-day intervals were given. One good day followed the first reaction. After the third shock the patient began spontaneous occupational activity, wrote letters and coöperated psychotherapeutically. A mood of mild elation followed the sixth treatment. After a period of 2 weeks of psychotherapy, the patient was dismissed with very good insight.

CASE 4.—Miss R. B., aged 37, developed a reactive depressive psychosis apparently precipitated by a disappointment in love. The patient had had a previous depression at 21 years; off work 1 year, she was not hospitalized. The mental status was characterized by marked anxiety; fear of cancer because of weight loss; tearfulness; desire to die; and self-accusatory delusions: "I am unfit to associate with others—the most wicked person on earth—can never get well—I'm going mad. I'm dirty and filthy," and so on. Attempts to ventilate the patient's problem only made self accusations worse.

A course of hematoporphyrin injections made no change in the mental state. Convulsive shock therapy was given. The patient failed to react by convulsions in about half the shocks. After these injections, more apprehension was present. But after 4 good convulsions, all evidence of severe depression disappeared. A mild anxiety state persisted, which was amenable to psychotherapy. The patient was dismissed 3 weeks after shock therapy was begun, in good condition.

CASE 5. Mrs. A. L., aged 60, was admitted in an acutely agitated stuporous state of 2 months' duration. Worry over economic and drouth factors on the farm seemed to start loss of sleep, anorexia and extreme agitation that culminated in an attempt to drown herself in a horse tank. The patient maintained a constant state of tearfulness, usually was mute and required spoon and tube feeding. Extreme self-accusation centered about ideas of an abortion in early life, with notions everything was gone—"family ruined, let me give myself up. I've made all the people sick. I'm so terrible. My son has gone crazy," and so on. At times the patient lay around on the floor and was careless of excreta.

During 2 months' observation, a course of theelin, 10,000 units dosage, and hematoporphyrin had been tried without improvement. The condition appeared to be growing worse. Convulsive shock therapy was begun. Five convulsions were induced at 3-day intervals. After the first convulsion, the patient fed herself for the first time. After the second shock, occupational activities were begun. The patient appeared completely relaxed and wrote letters to the family. From then on she became sociable, pleasant, smiled about everything and attempted to cheer up other patients. Describing her past worries as unimportant, she showed completely normal emotional reactions and was dismissed completely cured, 25 days after shock therapy was begun.

CASE 6. Mr. T. Mc., aged 64, became disinterested in work after financial reversals and an attempt to start business in a new location; he went to live with a son. Paranoidal ideas of his son's trying to get rid of him developed. Agitation, insomnia and suicidal threats caused his admission to the psychiatric ward. The mental reactions were characterized by agitation, apprehension, suspicion and refusal to adjust to any activities. He talked about an unhappy home life, past reversals and fears he would be poisoned or sent to the State hospital, since no one was interested in helping him. Numerous somatic delusions were present. He thought everyone about him had syphilis.

After 12 days of symptomatic treatment no evidence of improvement was noted and convulsive shock treatment was begun. The patient was extremely apprehensive over the treatment. Four convulsive shocks were given at 3-day intervals. After the first shock the patient joked and became less tense. He continued fearful of each injection but entered into ward activities, became jocular and no longer delusional. Because of angina-like complaints following the fourth injection, no more shocks were given. Electrocardiagraphic tracings were normal. The mental reactions continued normal and the patient was dismissed apparently well, 2 weeks after shock therapy was begun.

CASE 7. Mrs. E. F. C., aged 49, after a series of emotional shocks and a guilt conflict over a prolonged sexual problem, became depressed. Ideas of reference—self accusations and a progressive paranoidal trend—had been present for over a year. Because of loss of interest, brooding, withdrawal from active contacts and suicidal threats the patient was brought to the hospital.

Under observation for 30 days, during which time active estrogenic therapy was carried on, the patient continued to react with almost constant anxious and depressed attitudes. A strong religious drive with ideas of having committed the unpardonable sin, self-accusation over her recent marriage, with delusions of persecution referred to the husband's relatives, characterized the mental content. Somatic delusions related to syphilis and the pelvic organs were also present.

Convulsive shock therapy was advised; the patient reacted to convulsions with each injection. After the third injection, the patient began active occupational interests, laughed at jokes, and stated her past ideas were like a dream. Normal letter writing was begun; the patient accepted the treatment as beneficial and lost all evidence of former despondency. After the sixth injection the patient appeared entirely well. Two more weeks, hospital observation for reëducative psychotherapy was carried out and the patient dismissed.

CASE 8. Mrs. L., aged 35, had had a depressive breakdown at 21 years of age; gave up teaching for 9 months, and recovered. The present attack, of 4 months' duration, had begun after the death of her father. Psychogenic conflicts over a childless marriage, incomplete sexual adjustment and fear of pregnancy were also present. Progressive loss of interest, agitation, insomnia and self condemnatory ideas with suicidal threats caused hospitalization. The mental status was characterized by extreme agitation, and apprehension with panics that required sedative pack therapy and seclusion: "I can't stay here—no one can help me—I'm losing my mind—I'm responsible for my father's death," and so on. Two weeks' symptomatic sedative therapy, hydrotherapy and all attempts to establish a rapport or to interest the patient were unavailing. Exceedingly close observation was necessary on account of suicidal threats.

Convulsive shock therapy was begun. After the first convulsive seizure the patient dressed spontaneously, appeared relaxed and was cheerful in the afternoon. She stated that she "felt good." Slight relapses to the previously tense and agitated states occurred. After the second seizure, the tenseness and agitation again disappeared. The patient gradually became more and more coöperative in occupational and recreational therapy. The self-accusatory ideas disappeared and a constructive future program was planned. The patient was dismissed entirely well 48 days after shock therapy was begun.

CASE 9. Mr. W. S., aged 30, had a bad family history of depressive states. The patient had had two previous depressive attacks lasting 8 months to 1 year and in the last one had attempted suicide by gas poisoning. Following this, the patient had adjusted fairly well but had never recovered. One month prior to hospitalization he became acutely depressed and again attempted suicide. He also attempted to persuade a neurosurgeon to perform a prefrontal lobotomy, hoping for a fatal outcome. Under observation the patient was extremely restless, constantly complaining, appealing for help and threatening suicide. In panic states—"I can't stand it, give me a shot, knock me out, I'm losing my mind"—sedative packs were necessary.

Convulsive shock therapy was started and 7 injections given. The patient became relaxed and, after the second injection, coöperated well with occupation. Gradual improvement followed each injection. Financial strin-

gency and an unstable wife along with the patient's insistence that he was able to return to work led to his dismissal against advice. Following dismissal the patient found he had lost his position and when last seen was reacting at the level of an anxiety neurosis. The intense depressive features, however, seemed entirely gone. This was an incomplete recovery and the poorest result obtained of the entire group; yet, a very definite and marked improvement, to a point that psychiatric hospitalization was no longer necessary, followed the convulsive therapy.

Case 10. Mrs. B. E. H., aged 65, had been under treatment for 4 months in a psychiatric hospital in 1935 and 1936 on account of an agitated depression. This was characterized by ideas of self unworthiness, "lost soul," unpardonable sin and suicidal desire. Removal of focal infection, hematoporphyrin injections and estrogenic therapy along with symptomatic sedation resulted in an apparent improvement sufficient to permit the patient to adjust outside an institution, but complete recovery did not occur. The patient's daughter gave up school teaching to care for her. Frequent long trips were taken, but the patient never resumed social activities or charge of her household responsibilities. After 2 years there was no evidence that the depression would disappear.

The patient was returned for pentamethylenetetrazol shock therapy. Improvement followed each convulsive seizure and a mild hypomanic reaction occurred after the first three shocks. She developed active interest in the ward activities, and is still under hospital observation but the improvement seems to be following as noted in the other patients.

Comment on All Cases. The consistent change in the affects in all 10 of these severely depressed patients following convulsive shock leaves but little doubt that the treatment was responsible for the change.

A number of recommended therapies for depressive states (including insulin shock therapy) had been tried in the majority of these cases without influencing the course of the depression in any case before convulsive shock therapy was instituted.

The regularity of improvement within 2 weeks after pentamethylenetetrazol treatment was begun, even in severe types in the presenile period (Cases 2, 5, 6 and 10), speaks for the specificity of the method.

While we regard the method as potentially dangerous, particularly in the aged cases, no complications have resulted. We believe this treatment should be administered only under efficient psychiatric hospitalization and nursing protection. In older patients, careful investigation of cardiovascular function should precede therapy, which should not be instituted in cases showing myocardial or vascular disease.

We cannot explain the mechanism of recovery in these cases, but it is undoubtedly physiologic in nature and not psychologic. The circulatory change in the cerebrum resulting from the convulsions seemed to have some direct effect upon the emotional centers of the brain, alleviating anxiety and depression. The effect seemed strikingly similar to that described by the authors recommending prefrontal lobotomy.

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Sufficient time has not elapsed to determine delayed after-effects of the treatment or incidence of relapses. As far as could be determined, the recovered patients continue to be stable and normal.

Conclusions. Ten consecutive severe depressive psychotic patients have all been relieved by pentamethylenetetrazol shock therapy.

This method has more consistently shortened the depressive psychosis than any method heretofore described.

It is probable that the profound temporary change in cerebral circulation from induced convulsions alters physiologically the pathologic anxiety and depressive affective reactions. The result obtained is not entirely psychologic.

This method should be given further experimentation. It appears to be reasonably safe, even in older patients, but careful cardiovascular examination should precede its use. Its potential danger precludes its use for the present in general practice. It should be given only in well equipped psychiatric departments under skilled medical and psychiatric nursing supervision.

This treatment offers considerable hope of rapidly relieving the legions of suffering melancholiacs. There is also reason to believe the method may likewise become useful in severe anxiety psychoneuroses.

Eleven more patients, a total of 21 seriously depressed, have undergone convulsive shock therapy up to June 1, 1938. All of these showed marked improvement within 2 weeks after convulsive shock treatment began. Eight patients were past 55 years. No treatment complications were observed. One of involutional type had been a State hospital patient for over 2 years. All made social or complete recoveries. One relapsed in an acute manic excitement and was committed to a State hospital.

REFERENCES.

(1.) **Bennett, A. E.**, and **Cash, P. T.**: Nebraska State Med. J., **22**, 382, 1937. (2.) **Ellery, S.**: Med. J. Australia, **24**, 552, 1937. (3.) **Freeman, W.**, and **Watts, J. W.**: J. South. Med. Assn., **30**, 23, 1937. (4.) **Friedman, E.**: Am. J. Psychiat., **94**, 355, 1937. (5.) **Meduna, L.**: Arch. Neurol. and Psychiat., **35**, 361, 1936. (6.) **Menninger, K. A.**: Man Against Himself, New York, Harcourt, Brace & Co., 1938. (7.) **Moniz, E.**: Tentatives operatoires dans le traitement de certaines psychoses, Paris, Masson et Cie, 1936. (8.) **Montassut, M.**, and **Lemaire, A.**: Prog. méd., p. 1786, 1935. (9.) **Schächter, A.**: Gyogyaszat, **77**, 162, 1937; p. 182, 1937. (10.) **Schönmehl**: München. med. Wchnschr., **83**, 721, 1936.

BOOK REVIEWS AND NOTICES

PAVLOV AND HIS SCHOOL. The Theory of Conditioned Reflexes. By PROFESSOR Y. P. FROLOV, M.D., Member of the All Union Institute of Experimental Medicine, Moscow. Pp. 291; 27 illustrations. New York: Oxford University Press, 1937. Price, $4.00.

PAVLOV'S "Lectures on Conditioned Reflexes" has been so widely read even by those outside the scientific field and it covers the subject so clearly and adequately, that the indication for this early review of the material may well be questioned. The bulk of Dr. Frolov's book constitutes such a review and offers at least a partial answer to the query. In the new light which the later work of Pavlov and his school has thrown upon the interpretation of their older results such a reappraisal finds its best excuse. For most readers, however, the last chapter, an admirable essay in biography, is the part of the book that will be reread, for the sake of which they will not grudge it shelf room beside the work of the master who inspired it.

G. McC.

THE ANEMIAS. With Special Reference to Pernicious Anemia and the Use of Liver Extracts and Supplementary Factors in the Treatment of Anemias. Supplement. Blood Morphology in Diagnosis. A Series of Six Articles Reprinted from The Physician's Bulletin. Pp. 98; 7 colored plates. Indianapolis: Eli Lilly and Company, 1938.

THIS anonymous booklet has obviously been prepared by or with the help of a trained hematologist. It presents much useful and apparently accurate information, several good colored plates of characteristic blood smears, a section on diet in the anemias, and tables of standards and differential diagnoses. The advertising in the text, apparently essential to a "house publication," is limited to a comparatively few pages.

E. K.

PEDIATRIC SURGERY. By EDWARD C. BRENNER, A.B., M.D., F.A.C.S., Director of Surgery, Riker's Island and Detention Hospitals; Attending Surgeon, Midtown Hospital, etc. Pp. 843; 293 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

THIS volume, in which the author was assisted by well known workers in special fields, emphasizes the surgical lesions of pediatric practice. Special attention is given to diagnosis, indications for operations and end-results. In numerous instances operative procedures are discussed in detail and the important facts in regard to preoperative and postoperative treatment are thoroughly reviewed. The volume omits orthopedic conditions and operations for "these are well considered in many textbooks." The work is essentially in amplification of the author's lectures at the New York Post-Graduate Medical School of Columbia University.

There are 9 parts and 51 chapters covering nearly the entire field of general surgery. It may well be wondered at first, when so much of the diagnostic and therapeutic portion of the volume is a reiteration of material found in standard textbooks of surgery, why it should all have been included in this volume? However, the subject matter in this form of presentation reads so well that the Reviewer feels justified on the whole in commending

the method of presentation. Here and there in the text statements are made which are not in agreement with the Reviewer's surgical opinions. An instance of this is in the discussion of the "Choice of Incision" for acute appendicitis. There are many surgeons who prefer the pararectus incision for chronic appendicitis, but prefer the McBurney incision for acute appendicitis.

The work is voluminously illustrated with good clear illustrations. Occasionally an illustration appears to have been made from some one past the pediatric age, as in Figure 130.

Although the work is in reality a textbook of surgery it includes so much that it is of practical value in the treatment of surgical diseases of children that it should prove a valuable addition to surgical practitioners.

I. R.

DIE STÖRUNGEN DER SEXUALFUNKTION BEI MANN UND WEIB. VON DR. LUDWIG CHIAVACCI, Wien. Mit einem Geleitwort von PROF. DR. OTTO PÖTZL. Pp. 146. Wien: Franz Deuticke, 1938. Price, Paper, M. 4.60; Bound, M. 5.40.

THIS monograph should prove to be indispensable to those physicians who are called upon to deal with functional sexual difficulties, as diagnosis and therapy rest on the firm basis of physiology and pathology. The author purposely avoids the psychoanalytic pitfalls of psycho-sexual disturbances and very wisely states that the organic-physiologic basis of these disturbances must first be recognized and evaluated before the problem is approached from the psycho-therapeutic viewpoint. B. H.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis, Minn. Pp. 894; 412 illustrations and 2 colored plates. Third Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $9.50.

IN this third edition there are 127 more pages, more references have been added, and there are 62 excellent new illustrations. The general plan of the previous editions has been retained, but revisions in the text have been made throughout. The presentation is systematic and clear, heavy print attracts the eye to the important headings, and illustrations derived from the practice of pathology are very convincing. These modifications should greatly increase the usefulness of this textbook in fulfilling the aims of its author to furnish students of pathology with a sound basis for clinical medicine. I. Z.

THE TRUTH ABOUT CHILDBIRTH. Lay Light on Maternal Morbidity and Mortality. By ANTHONY M. LUDOVICI. Pp. 294. New York: E. P. Dutton & Co., Inc., 1938. Price, $2.50.

THE author, a well known sociologist of England, advances in this book the theory that childbirth should not be regarded in other than the light of a consciously pleasant experience. In developing the thesis he discusses the factors which have influenced a state of mind among women and physicians that pregnancy is a disease of 9 months, with delivery as the catastrophic climax to the disease. Simultaneously he brings out support to favor directly his contention that the frequent abnormalities of pregnancy and delivery are not essential and can be removed.

The first part of the book discusses the influence of increasing intelligence,

the feministic trend of thought and the economic conditions of the world today on reproduction, and describes the physiology of normal childbirth.

The second part discusses those conditions which conflict with painless and pleasurable birth. These include the factor of age at the time of delivery of the first child, the effect of late marriages, athleticism, miscegenation, the mixture of types and statures and nutritional deficiencies of the present day diet.

Further the author describes the primitive postures in childbirth, the relationship of modern habits of life on delivery and the demand for and effect of analgesics and anesthetics in labor. The book is profusely documented in a remarkable review of the literature dealing with the sociologic aspects of reproduction.

There are many intriguing statements and deductions brought out with which all obstetricians probably will not agree; but it may certainly be admitted that the text is extremely interesting in the discussion of many problems faced in present day obstetrics. P. W.

HEMORRHOIDS. By MARION C. PRUITT, M.D., L.R.C.P., S. (ED.), F.R.C.S. (ED.), F.A.C.S., Atlanta, Georgia, Associate in Surgery, Emory University School of Medicine; Proctologist, Grady, Crawford W. Long Memorial, and Georgia Baptist Hospitals, etc. Pp. 170; 73 illustrations. St. Louis: The C. V. Mosby Co., 1938. Price, $4.00.

THE author, regarding the treatment of hemorrhoids as still a live subject, attempts here to describe and evaluate the various methods of treatment. The first part of the book discusses the embryology, surgical anatomy and physiology of the lower rectum and anal canal. Then follows a section on examination of the patient and the instruments used. In speaking of anesthesia, the author recommends a general anesthetic or a local infiltration anesthesia with nupercain 1 to 1000 solution. He believes that spinal anesthesia is indicated in only certain selected cases, and caudal or transsacral block is a tedious and time-consuming method. He briefly discusses the pathology of hemorrhoids and classifies them in what appears to the Reviewer to be an unnecessarily complicated manner. Considering treatment, he recommends immediate operation for thrombosed external hemorrhoids, but is in favor of conservative therapy for inflamed or strangulated internal hemorrhoids. He reviews the history of injection treatment and describes his own technique. He uses 5 to 12% solution of carbolic acid in a vehicle of equal parts glycerin and water and injects 3 to 10 drops into the center of each hemorrhoidal mass. If the injections are submucous he uses 1 to 6 cc. of 5 to 10% solution of phenol in vegetable oil. He recommends that all the internal hemorrhoids be injected at each treatment through a short tubular speculum. When injecting into the center of the mass, the needle is allowed to remain in place for about a minute after injection. The author believes that edema "occludes the needle puncture in most cases immediately following the withdrawal of the needle and tends to prevent backflow of the solution." Injections are given 5 to 10 days apart and an average of 4 to 5 treatments are given. Pruitt places recurrences following injection at from 15 to 20% as compared with 5 to 8% recurrence following operation. In his chapter on operative treatment of internal hemorrhoids he describes his own technique as well as the well-known operations of Buie, Lockhart-Mummery, Tuttle and Whitehead. He mentions the use of galvanism and of high-frequency currents in the treatment of hemorrhoids only to condemn them. The book contains many original illustrations, some in color. It will probably be useful to those who are interested in proctology. L. F.

CHRISTIANITY AND SEX. By RICHARD C. CABOT, M.D. Pp. 78. New York: The Macmillan Company, 1938. Price, $1.00.

CONTINUING a long and distinguished career in scientific medicine, the author has in recent years also contributed notably toward illuminating the borderline between the physician and his patient. "Honesty," "The Layman's Handbook of Medicine," "What Men Live By," "The Meaning of Right and Wrong," and "The Art of Ministering to the Sick," are not only much needed expositions of an experienced and intelligent, 20th century Puritan's principles of morals but also valuable interpretations of medical advances in terms understandable by the laity. This, his latest work, frankly and firmly emphasizes that the Christian spirit must be the guide to the solution of the problem of sex. Knowledge of sex hygiene is of little help; medical men and nurses are no more or no less chaste than others of similar intelligence. Throughout the 4 chapters he emphasizes that a Christian attitude is of more importance in sex matters than set rules of conduct, that sex relationships have as important spiritual as physical sides, that life, "the greatest word in the Christian vocabulary," may be had more abundantly by the fullest union of body and spirit. Available reinforcements of "the consecrated affections" are suggested; but attempts to deal with the "original sin" of desire are, perhaps necessarily, incomplete. If the average person could attain the intense religious spirit of the writer, not only would sex cease to trouble but the world would be a very different and better place to live in. E. K.

A TEXTBOOK OF CLINICAL PATHOLOGY. Edited by ROY R. KRACKE, B.S., M.D., Professor of Pathology, Bacteriology and Laboratory Diagnosis; Chairman of the Department, Emory University; Pathologist to the University Hospital. With the assistance of 11 Additional Contributors. Pp. 567; 205 illustrations and 31 plates (19 in color). Baltimore: William Wood & Co., 1938. Price, $6.00.

THIS is an excellent, practical, comprehensive, up-to-date textbook of clinical laboratory diagnosis, by an all-Southern group of teachers representing the Universities of Georgia, Tennessee, Texas, Alabama, Louisville and Arkansas, Emory, Vanderbilt and Tulane Universities, and The Medical College of the State of South Carolina. The Reviewer, trying hard to find something to criticize, suggests that the Dare hemoglobinometer is given a less critical rating than it deserves (p. 117), the figures illustrating the blood picture of pernicious anemia "in remission" (p. 198) should be omitted, raised to normal or labelled "Blood Picture in Unsatisfactory Remission or Partial Relapse" and the figures (pp. 199 and 200) illustrating "Blood Picture under Liver Therapy" should be entitled "Blood Picture at End of First Week of Liver Therapy." The chapters are well correlated and documented. The index, figures and plates are good. The book is highly recommended for students, internes, laboratory technicians and practising physicians. T. F–H., JR.

BILE. ITS TOXICITY AND RELATION TO DISEASE. By O. H. HORRALL, M.D., PH.D., F.A.C.S., Department of Physiology, The University of Chicago. With a Foreword by A. J. CARLSON, M.D., University of Chicago. Pp. 434. Chicago: The University of Chicago Press, 1938. Price, $4.00.

THIS monograph, the second on the bile to be published in this country during the year, aims to summarize and analyze the physiologic and toxic actions of bile as revealed by past observations and experiments. The author states that "no critical summary of our modern knowledge of the

composition of bile and its relation to disease is available." Surely Ivy's excellent critical summary of the subject in *Physiological Reviews* must have been overlooked.

There are 27 chapters, a bibliography and an index. An attempt is made to cover every aspect of the subject from the "History of Bile" to the "Therapeutic Effects of Bile Acids." The volume reviews a great mass of experimental and clinical observations. As an encyclopedia of the literature on the subject of the bile, it will prove useful to workers in the field; but to those whose knowledge of the subject does not permit them to pass judgment on reviews of material, the volume may prove to be misleading. This is especially true of chapters such as the one on "Origin of the Bile" where many conflicting observations are reported and only rarely does the author state his opinion, based upon his work on the bile and his judgment as an investigator.

The bibliography consists of 2177 references, and, therefore, is the largest available. The work will prove very valuable to anyone interested in the many problems of the bile for to them it will be a *vade mecum* of the literature on the subject. I. R.

NEW BOOKS.

The British Encyclopedia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Vol. 7. Hyperchlorhydria to Leucorrhœa and Other Non-hæmorrhagic Vaginal Discharges.* Under the General Editorship of Sir Humphry Rolleston, Bt.G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. Fraser, M.D., F.R.C.P., G. Grey Turner, D.Ch., M.S., F.R.C.S., James Young, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., Sir Leonard Rogers, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 759; 171 illustrations. London: Butterworth & Co., 1938. Price, $12.00.

Among the more important articles in this volume are those on Impetigo (22 pages), Influenza (18 pages), Intelligence Tests (12 pages), Joint Diseases (43 pages), Kala Azar (36 pages), Surgical Diseases of the Kidney (34 pages), Labor (178 pages), Larynx Diseases (29 pages).

Injection Treatment of Varicose Veins and Hemorrhoids. By H. P. McPheeters, M.D., F.A.C.S., formerly Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital; Attending Physician, New Asbury, Fairview and Northwestern Hospitals, Minneapolis, and James Kerr Anderson, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Fellow, American Proctologic Society, etc. Pp. 315; 82 illustrations. Philadelphia: F. A. Davis Company, 1938. Price, $4.50.

The Doctrine of Signatures. A Defence of Theory in Medicine. By Scott Buchanan. Pp. 201. New York: Harcourt, Brace & Co., 1938. Price, $2.75.

Polski Przeglad Radiologiczny, Tom. XII, Nr. 3/4. Edited by Dr. W. Zawadowski, Warsaw. Pp. 693; many illustrations. Warsaw: Nakl. Polskiego Lekarskiego Tow. Radio. I. Fizjoterap., 1937.

Salaries in Medical Social Work in 1937. By Ralph G. Hurlin, Director, Department of Statistics, Russell Sage Foundation. Pp. 34. New York: Russell Sage Foundation, 1938. Price, 20c.

The Fight for Life. By Paul deKruif. Pp. 342. New York: Harcourt, Brace & Co., 1938. Price, $3.00.

Lehrbuch der Pharmakologie, Toxikologie und Arzneiverordnung. Unter Mitarbeit von Prof. Dr. med. et rer. nat. HEDWIG LANGECKER, Dr. med. FRANZ HENDRYCH, Dr. med. et rer nat. et mag. pharm. KARL KLIMESCH und Dr. rer. nat. et Dipl. Ing. HANS WEDEN. By DR. MED. EMIL STARKENSTEIN, o. ö. Prof. der Pharmakologie und Pharmakognosie an der deutschen Universität in Prag. Pp. 758; 40 illustrations. Wien; Franz Deuticke, 1938. Price, Paper, M. 20; Bound, M. 23.

Zum Krebsproblem und Verewandten Gebieten. Infektion, Regeneration, Zellmutation, Befruchtung. Von DR. FRITZ NIEDERMAYER, Chefarzt und Leiter der chirurgischen Abteilung des Krankenhauses Passau. Pp. 166. Wien: Franz Deuticke, 1938. Price, Paper, M. 5; Bound, M. 7.

Vitamin B_1 (Thiamin) and Its Use in Medicine. By ROBERT R. WILLIAMS, Sc.D., of the Bell Telephone Laboratories, New York City, and TOM D. SPIES, M.D., Associate Professor of Medicine, University of Cincinnati. Pp. 411. New York: The Macmillan Company, 1938. Price, $5.00.

Sulfanilamide Therapy of Bacterial Infections. With Special Reference to Diseases Caused by Hemolytic Streptococci, Pneumococci, Meningococci and Gonococci. By RALPH R. MELLON, M.D., DR. P.H., D.SC. (HON.), Director, Institute of Pathology, The Western Pennsylvania Hospital, Pittsburgh; PAUL GROSS, M.D., Pathologist to the Institute; and FRANK B. COOPER, Research Chemist to the Institute. Pp. 398; 16 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, $4.00.

The Construction of Vulcanite Applicators for Applying Radium to Lesions of the Buccal Cavity, Lips, Orbit and Antrum. By DESMOND GREER WALKER, M.A., M. DENT. SC., M.B., B.CH., Assistant Dental Surgeon to the Royal Dental Hospital; Dental Registrar at the Middlesex Hospital, etc. Foreword by W. WARWICK JAMES, O.B.E., F.R.C.S., L.D.S. Pp. 61; 2 illustrations and 22 plates. London: John Murray for the Middlesex Hospital Press, 1938. Price, 5/–.

A Bibliography of The Works of Ambroise Pare: Premier Chirurgien & Conseiller du Roy. By JANET DOE, Assistant Librarian of the New York Academy of Medicine. Pp. 265; 30 illustrations. Chicago: The University of Chicago Press, 1937. Price, $5.00.

Clinical Roentgenology of the Digestive Tract. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, University of Maryland; Associate Roentgenologist, Sinai Hospital; Assistant in Gastroenterology, Mercy Hospital, Baltimore. Pp. 1014; 358 illustrations. Baltimore: William Wood & Co., 1938. Price, $10.00.

The Harvey Lectures, Series XXXIII. Delivered under the Auspices of the Harvey Society of New York, 1937–1938. Under the Patronage of the New York Academy of Medicine. By DRS. SELIG HECHT, EINAR LUNDESGAARD, CECIL K. DRINKER, JOHN P. PETERS, PHILIP BARD, WENDELL M. STANLEY, F. C. KOCH, HARRY GOLDBLATT. Pp. 275; 60 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, $4.00.

Clinics on Secondary Gastro-intestinal Disorders; Reciprocal Relationship. By JULIUS FRIEDENWALD, M.D., Professor Emeritus of Gastro-enterology, THEODORE H. MORRISON, M.D., Clinical Professor of Gastroenterology, and SAMUEL MORRISON, M.D., Assistant Professor of Gastroenterology, University of Maryland, School of Medicine. Pp. 251. Baltimore: William Wood & Company, 1938. Price, $3.00.

Memorandum Book of a Tenth Century Oculist for the Use of Modern Ophthalmologists. A Translation of the Tadhkirat of Ali ibn Isa of Baghdad (cir. 940–1010 A.D.), the most complete, practical and original of all the early textbooks on the Eye and Its Diseases. The First Edition in English, by Casey A. Wood. Pp. 260; 21 illustrations. Chicago: Northwestern University, 1936. Price, $8.00.

NEW EDITIONS.

Diseases of Women. By Ten Teachers, Under the Direction of CLIFFORD WHITE, M.D., B.S. (LOND.), F.R.C.P. (LOND.), F.R.C.S. (ENG.), F.C.O.G. Edited by SIR COMYNS BERKELEY, CLIFFORD WHITE and FRANK COOK. Pp. 492; 159 illustrations and 7 colored plates. Sixth edition. Baltimore: William Wood & Co., 1938. Price, $6.00.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Consulting Physician, International Clinic, Tunbridge Wells; Assistant Physician, St. Mary's Hospital for Women and Children, etc.; and STANLEY WARD, M.D., M.R.C.P., Physician, The Royal Cancer Hospital, London, and Princess Beatrice Hospital. Pp. 127; 42 plates (38 in color). Fourth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $4.50.

A Textbook of Physiology. By WILLIAM D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Pp. 714; 291 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $4.00.

Materia Medica. Drug Administration and Prescription Writing. By OSCAR W. BETHEA, M.D., PH.G., PH.M., F.C.S., F.A.C.P., Professor of Clinical Medicine, Tulane School of Medicine; Professor of Therapeutics, Tulane Graduate School of Medicine, etc. Pp. 577. Fifth revised edition. Philadelphia: F. A. Davis Company, 1938. Price, $5.00.

Electrotherapy and Light Therapy. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Physician-in-Charge, Physical Therapy, City Hospital, New York, etc. Pp. 744; 307 illustrations and 1 colored plate. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $7.50.

Diseases of the Nose, Throat and Ear. Medical and Surgical. By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., Late Professor of Otology, Rhinology and Laryngology, College of Medicine, University of Illinois, Chicago, etc., and HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Ill., etc. Pp. 1030; 576 illustrations and 30 plates. Seventh edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $11.00.

Medical Jurisprudence and Toxicology. Edited by JOHN GLAISTER, M.D., D.Sc., Barrister-at-Law, Regius Professor of Forensic Medicine, University of Glasgow, etc. Pp. 747; 107 illustrations and 8 plates. Sixth edition. Baltimore: William Wood & Co., 1938. Price, $8.00.

The Foot. By NORMAN C. LAKE, M.D., M.S., D.SC. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 366; 353 illustrations. Second edition. Baltimore: William Wood & Co., 1938. Price, $4.50.

Handbook of Practical Bacteriology. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh; Honorary Bacteriologist to the Royal Infirmary, Edinburgh, etc., and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, London County Council, etc. Pp. 586. Fifth edition. Baltimore: William Wood & Co., 1938. Price, $4.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
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PRIMARY CARCINOMA OF THE LUNG.

DURING the past few decades, clinicians, pathologists and medical statisticians have all been focusing their attention on carcinoma of the lung as a condition deserving of intensive investigation. The results of this scrutiny are to be found in the mass of literature which has been accumulating at an ever-increasing rate, and which has been responsible for a marked change in attitude toward this peculiarly interesting condition. Though all phases of the question have been extensively studied since the recording of Morgagni's case[64] in 1761 and Bayle's "phthisie cancéreuse"[7] in 1810, it may still be difficult for the casual reader to obtain a clear picture of the subject as a whole, being faced on the one hand by detailed compilations of data and on the other by brief case reports, or writings dealing with a limited or narrow phase of the problem. Textbooks are likewise of little help, particularly those of a clinical nature which tend to dismiss the matter with extreme brevity, merely emphasizing the rarity of the disease and the difficulties associated with the diagnosis. But it must be borne in mind that in reviewing briefly a subject such as bronchial cancer, little can be done other than to trace the evolution and moulding of opinions regarding the condition. This is in sharp contrast with the field of experimental medicine where controlled observations point to incontestable conclusions. No attempt has been made in the present paper to review the whole literature of carcinoma of the lung. References will be made only to those publications which would appear to be the most authoritative and which most clearly demonstrate the trend of modern thought.

Incidence. Carcinoma of the lung can no longer be considered a rare condition as was frequently stated, even as late as 1922.[6] The

present incidence of the disease has attained a high position among all neoplasms. Barron[6] found carcinoma of the lungs and bronchi ranked sixth among all malignancies, while Rosahn[72] placed it fifth. Rosedale and McKay[73] found carcinoma of the lung the third-commonest cancer encountered in a series of 466 cases of malignancy of all types. Brines and Kenning[12] placed the lung second to stomach as a seat of primary malignant neoplasms in their necropsy material and fifth in their surgical specimens. Simpson[82] found pulmonary cancer constituted 3.7% of his autopsies, while other figures vary from about 1 to 4% of all postmortems.[9a,b] From the observations made in the Department of Pathology at the University of Toronto over a 10-year period ending in 1936, the lungs and bronchi proved the third-commonest site for malignant epithelial tumors as seen at autopsy, being preceded only by the large bowel (including the rectum) and the stomach. Indeed, 1.17% of all autopsies were cases of bronchial cancer, which in turn constituted 17% of all cases of carcinoma. Though it is difficult to determine the actual present-day incidence of the disease, it must be considered comparatively common, while pulmonary tumors of other than a carcinomatous nature are now looked upon as being relatively rare.[21]

Nearly all are agreed that the condition is encountered with greatly increased frequency, and this has raised the controversial question of whether the increase is actual or apparent. In a survey of much of the European literature on the subject, Bonser[9b] found a reported increase in the condition in 32 instances, a slight increase in 5 and no increase in only 8. Wahl,[93] from 1895 to 1927, found an increase in the incidence of cancer of the lung from 0.44 to 1.69% of all autopsies; Duguid,[19] from 1885 to 1926, observed an increase from 0.24 to 2.57%; Kikuth,[47] from 1889 to 1923, showed an increase from 0.02 to 0.86% and Barron,[6] from 1889 to 1921, an increase from 0 to 0.9% and so on. The increased frequency with which the disease is recognized is further emphasized when one considers that Adler,[1] in 1912, was able to collect but 374 authenticated cases, whereas a complete present-day summation would number thousands with some reports, including a hundred or more from a single source.

A few investigators believe that no increase has occurred in the incidence of carcinoma of the lung. Thus, Bonser[9a,b] was unable to demonstrate any change in the incidence of the condition in relation to total autopsies, total cancers, or hospital admissions at the Leeds Infirmary. Though this worker did observe that the highest incidence occurred during the 5-year period ending in 1932, this was only slightly in excess of the incidence for the 5 years from 1908 to 1912. Similarly, Passey and Holmes,[68] in a carefully controlled analysis of the available statistics from some of the teaching hospitals of Great Britain, found no increase in the incidence of carcinoma of the lung in 8 instances and a variable increase in 8 others. These writers considered that the increased incidence found in these latter was the result of special circumstances and did not indicate a real change. The statistics from several of these hospitals, from which it was deduced that no increase had occurred, had previously been reported in a different form[19] and had been considered indicative of an actual increase.

Despite such reports as the foregoing, the great majority of authors

are agreed that the condition is now seen more commonly than formerly. Most of them, however, consider the increase purely apparent and offer a variety of reasons in explanation of this. Important among these are the increased span of human life, and increased interest in the condition stimulated by both improved diagnostic equipment and the hope of carrying out successful intrathoracic surgical procedures.[4,14,21] Other important factors are fashion in diagnosis[46] and the changed attitude of the pathologist who now recognizes to be actually primary carcinomata pulmonary lesions formerly considered metastatic, sarcomatous or inflammatory.[5]

It is obvious that increase in longevity, by allowing more people to reach the cancer age, should be accompanied by an increase in cancer in general. That this might be considerable can be appreciated when it is realized, as has been pointed out by Fried,[29c] that the average span of life from the time of Tut-Anhk-Amen to the discovery of America was only 18 years, at the time of the French Revolution (1789–1799) 33 years, and at the time of the Civil War (1861–1865) still only 45 years.[88] At present the average length of life is in the neighborhood of 58 years. Corresponding with this increase in longevity, an apparent increase in the incidence of cancer in general has occurred, as pointed out by Wells,[95] who indeed considers that a "high crude cancer death rate is evidence of a good state of public health." Wells further states that cancer has probably increased only to the extent that people are kept from dying of other conditions. Despite the fact that graphs can be prepared to show a parallellism between the increased life span, increase in cancer in general and increase in cancer of the lung in particular (as has been well done by Hruby and Sweany[41]) many observers have found that the increase in lung cancer has far outstripped the increase in all others,[72,94b] and this precludes an explanation of the increase of cancer of the lung on the basis of increased expectancy of life alone.

There can be no doubt that clinical interest has been stimulated by the development of Roentgen ray, bronchoscopic and biopsy techniques, and by the more consistent recognition of bronchial carcinomata by the pathologist at autopsy. The effects of this interest, however, on autopsy statistics must be indirect and possibly slight, depending upon increased zeal in obtaining autopsy permission, and also, the keeping of patients with such lesions in hospital up to the time of death at the expense of many of the less interesting and better understood cases.[82]

Although Simpson[82] doubted that any improvement in clinical diagnosis had occurred, and indeed found the greatest clinical error in the year 1924, the vast majority of investigators have noticed a great change. Bonser[9a] noted an increase in the frequency with which the clinical diagnosis was made from 0.127 to 0.253% of all hospital admissions over a period of 41 years, while the incidence at autopsy remained constant. Weller,[94a] in 1913, found a correct diagnosis had been made in 11% of his cases; none of those reported by Scott and Forman,[78] in 1916, were recognized clinically; but Brines and Kenning,[12] in 1937, found a correct diagnosis had been made in 73% of their series. One reason for this improvement in diagnostic skill is the many additional aids available to internists.[16] Actually the value of the Roentgen ray, with or without the use of iodized oil, is questioned by some,[58] and

Fishberg[26b] considers a careful history and physical examination of much greater importance, particularly in the recognition of early cases. Histologic studies on sputum and pleural fluids are occasionally of assistance, but are of more use in ruling out tuberculosis and other infections.[94b] Such examinations may also prove misleading, as is clearly shown in the case reported by Mills and Mumey[62] which was originally mistaken for a case of Entamœba histolytica infestation. Bronchoscopy has proved the most valuable diagnostic aid as yet offered and has led to the recognition of many obscure cases.[58,94b]

Even with the numerous technical methods now available, it still rests with the internist to recognize the indications for their use. Probably many missed diagnoses were formerly the result of failure to think of bronchial tumors. Physicians are now, however, rapidly coming to realize that carcinoma of the lung must be included in their differential diagnosis when a patient in the "cancer age" presents himself complaining of loss of weight, cough, dyspnea, chest pain and blood-tinged sputum.[26b,28,90]

The third and one of the most important arguments favoring the conclusion that the increase in lung cancers is apparent rather than real has to do with the changed attitude of the pathologist. With the advent of bacteriology, and especially the identification of the tubercle bacillus, a sound basis was available for the differentiation of infectious granulomata from lung tumors, and probably many old cases, formerly classed as tuberculous, were actually neoplastic. With our present knowledge of the characteristics of the two conditions, it is seldom that they could be confused on gross examination and never on the basis of microscopic study. Some difficulty may arise, however, when the lesions are coëxistent.

A further great step was made in the pathology of intrathoracic tumors with the recognition of the carcinomatous character of tumors formerly considered sarcomata of one kind or another. The gross characteristics of many primary bronchial growths, their tendency to form large mediastinal masses and to give rise to bizzare metastases was probably misleading. Likewise, the microscopic picture may, and often does, closely simulate that of a sarcoma. These were possibly the sources of error responsible for the astonishing conclusion reached by Rolleston and Trevor,[71] in 1903, that sarcoma of the lung was commoner than carcinoma of the lungs and bronchi. In the light of our present knowledge, it is easy to identify as probably carcinoma, cases once reported as being sarcoma, such as those of Stevens[86] who considered carcinoma of the lung rarer and sarcoma commoner than was thought even at that time (1912). Adler[1] referred, in 1912, to the tendency of lung cancers to assume a sarcomatous form, while in 1926 Barnard,[5] after studying the nature of "oat-celled sarcoma" of the mediastinum, concluded, on the basis of both gross and microscopic appearance, that these were actually bronchial carcinomata. He observed 12 cases of oat-cell tumor, all of which showed, in addition, areas composed of cells which were indistinguishable from those of an epithelial type. More recently Boyd,[10] using the special silver stains of Hortega (Laidlaw's modification), satisfied himself as to the epithelial nature of these cells largely on the basis of the reticular arrangement. Duguid[19] found many of the cases he reviewed had previously

been classed as lymphosarcomata. Though Weller[94b] found a decrease in the incidence of sarcoma of the lungs concomitant with the increase in cancer, the number of sarcomata was too small to explain alone the increasing incidence of the epithelial growths. Frequent emphasis is laid upon the necessity of cutting numerous histologic sections from these sarcoma-like tumors,[5] thus greatly increasing the chances of establishing indubitably the epithelial character of the tumor. Similarly, it has been observed[82] that if a sufficiently diligent search is made in bronchial cancers of a well-differentiated cell type, areas of tumor composed of small, anaplastic, sarcoma-like cells will be found in almost all of them.

The dictum of Virchow and of Lubarsch that organs to which tumors were prone to metastasize were seldom the sites of primary growths, may have had considerable influence on the older pathologists, especially since the lungs were considered a typical example of an organ in which secondary tumors were common and primary malignancy correspondingly rare.

Though some authors consider it unsafe to say whether the increase in lung tumors is real or apparent,[33] others suggest that the latter is actually the case.[6,19,50,72,82,94b] One of the strongest arguments favoring the conclusion that the increase is real, at least in part, is to be found in the reports of increased incidence coming from institutions which have been under the same supervision and have required the same standards of diagnosis for a number of years. An increase under such conditions has been reported by Rosahn,[72] Weller,[94b] Barron,[6] Klotz,[50] Simpson,[82] Duguid,[19] Hunt[43] and many others, and forms, in part, the basis of their belief in the reality of the increase. The majority of these workers also believe that the arguments offered in explanation of the change being purely apparent are not sufficiently convincing to allow any final conclusions in that regard.

Statistics have been avoided, as the Reviewer is inclined to agree with the somewhat pessimistic opinion of Wells[95] as to their value. Their significance is further questioned when we find, as pointed out by Frissell and Knox,[31] that Rosahn and Fried, using the same statistical material, came to opposite conclusions. Similarly, Kikuth[47] and Breckwoldt,[11] using the same and analogous material, also came to opposite decisions, as has been previously mentioned by Bonser.[9a] Likewise, Passey and Holmes,[68] in reviewing the same material as Duguid,[19] were unable to support the original conclusion that a real increase in the incidence of lung cancer had occurred.

It would appear, however, that much of the increase in bronchial carcinoma is apparent. How much of the increase is real will probably never be known, the world never having been in the state of a pathologist's Utopia where necropsy routinely follows death. Similarly, the true present-day incidence is uncertain, but nevertheless the condition must be considered sufficiently common and important to warrant the attention it has been shown.

Anatomic Varieties. At one time it was customary to differentiate between bronchial cancer and cancer of the lung parenchyma.[39,69] This distinction can, however, for all practical purposes be discarded in favor of the modern view that they are one and the same. Indeed, Weller[94a] required, in order to consider a case proven, good evidence of

bronchial origin in addition to other stipulations. Simpson[82] points out that the condition cannot be diagnosed with certainty macroscopically. This is particularly true as regards the diffuse form to be referred to below. But when it has been established that an intrathoracic tumor exists, carcinoma of the lung must be differentiated from sarcomata, pleural tumors, carcinoma of the esophagus extending to involve the lungs, metastases from inconspicuous primary growths and inflammatory lesions.[82]

Gross Anatomy. The gross appearance of bronchial carcinomata is extremely variable and yields little information as to the cell type to be found microscopically; hence a gross classification is highly unsatisfactory.[44] It is usual, however, to group them macroscopically as: 1, Infiltrating hilar; 2, nodular, single or multiple; and 3, diffuse. Such a grouping as this, suggested by Fishberg[26b] and Weller,[94b] and indeed adopted by most pathologists, is considered as unsound by Fried,[29d] who records several cases to support this point. Fried considers that nearly all these carcinomata originate in close relationship to the hilum. He further doubts that any purpose is served by separating the diffuse and nodular forms, considering these to be mutually transposable. Despite this criticism some form of general gross grouping is desirable and useful.

The hilar infiltrating form is by far the commonest, and according to Weller[94b] probably constitutes about 90% of all bronchial growths, though Frissell and Knox[31] classified only 49% of their cases as such. Tumors of this type tend to form masses about the bronchi, usually at the root of the lung, with stenosis and ulceration of the lumina, and to extend peripherally around the blood-vessels, bronchi and over the pleura so as eventually to involve the major portion of a lobe or lung. It is this form that frequently gives rise to massive involvement of the peribronchial and mediastinal lymph nodes, which may attain an enormous size, while the primary growth may remain comparatively small.[82,94b] The consistency of these hilar infiltrating growths is highly variable, depending largely, as is true of carcinomata elsewhere, on the cellularity of the growth, the density of the stroma and the extent of necrotic changes within the tumor. Frequently, hilar tumors are encountered with stenosis but no ulceration of the bronchus, and these often prove to be of a mucoid nature both in their gross and microscopic appearance.[1,63,82]

The nodular form of primary lesion is comparatively rare. Usually this takes the form of multiple small circumscribed masses scattered through the lung parenchyma, varying from the size of a pinhead to that of a bean or larger and tending to coalesce in the advanced stages. It is frequently difficult or impossible to demonstrate any gross relationship of the tumor to bronchi. Thus there arises considerable difficulty in ruling out multiple metastases from an obscure primary growth. This is particularly true when the nodules are scattered uniformly throughout both lungs, rather than being confined to one portion of a lobe or lung. The multiplicity of nodules of fairly uniform size has led many to consider this as evidence of a multicentric origin.[37] A rarer form of the nodular type is the single, peripherally located growth described by Adler.[1] These are exceedingly rare but the

Reviewer has observed 1 such case. It is probable that these arise from the peripheral rather than hilar bronchi.

The diffuse form is also comparatively rare and, indeed, doubt has been expressed by some as to its actual existence, considering it merely a variation of the usual picture and not an entity in itself.[29d] Here the gross appearance of the lung may closely simulate a pneumonic consolidation or interstitial fibrosis and the true nature of the process may not be recognized until microscopic study is carried out. Even then, all other possible sources must be excluded before one concludes that the tumor originated within the pulmonary tissues. Frequently these growths prove to be composed of cuboidal or cylindrical cells growing in a papillary adenomatous manner and lining the air spaces. This is the picture usually referred to when a pulmonary tumor is said to have had its origin in the lining cells of the alveolar spaces. Two such cases have been observed by the Reviewer. In one of these, the involved lung showed nothing in the gross other than collapse associated with a massive serous pleural effusion. In the second case, the appearance of the lung was typical of a chronic organizing pneumonia. It is of considerable interest that in both these cases a correct clinical diagnosis was made but could not be confirmed at autopsy until examination of microscopic sections revealed the diffuse malignant processs.

The secondary effects produced by a bronchial tumor are often extensive and may at times be confusing. Most of these are the result of interference with respiratory function, obstruction to the drainage of bronchial secretions and infection. These factors may lead to atelectasis, fibrosis, bronchiectasis, lung abscess, empyema, pneumonia and occasionally emphysema.[26b,29d,94b] Often the symptoms resulting from these changes dominate the clinical picture.

Histogenesis. A histogenetic grouping of pulmonary tumors is even less satisfactory than a gross classification. This is due in part to the infrequency with which extremely early growths are encountered where their origin can be traced, and in part due to the inconstant histologic picture presented by the growths. Despite this, histogenesis is used by some as a basis for classification.[24]

The epithelial elements of the lung from which carcinomata might arise consist of the bronchial mucosa and glands and the alveolar lining cells.[60] The bronchial mucosa is composed of the superficial cylindrical cells (which are mostly ciliated, goblet cells occurring only at intervals), an intermediate layer of replacement cells and the basal formative cells.[63] The bronchial mucous glands and their ducts are lined by cylindrical, non-ciliated, mucous and seromucous secreting cells. Passing down the bronchial ramifications to the terminal bronchioles, the lining epithelium becomes lower and lower, cilia and goblet cells disappear, until finally in the respiratory bronchioles it is composed of a single layer of low cuboidal or flattened cells.[60,63] A further transition occurs in the alveoli where the lining cells are of a flattened type. The peculiar activities of these cells have led many[29b,60] to doubt their epithelial character. Recently, however, on the basis of animal experimentation, Gazayerli[33] concluded that the normal lining consists of flattened, nucleated, epithelial cells and, in addition, scattered cuboidal cells of the reticulo-endothelial system with a phagocytic function (septal cells).

The difficulty in classifying pulmonary cancers in relation to these cell types arises from the fact that there is usually little resemblance between the tumor cells and normal pulmonary structures, and thus a histologic connection is difficult to establish. The greatest difficulties are encountered in the undifferentiated small-cell carcinomata and the completely differentiated epidermoid tumors with pearl formation. Furthermore, many growths show pleomorphic tendencies, and adenomatous, epidermoid and sarcoma-like areas may be found in the same tumor or even in the same section.[5,50,58]

Actually, the ability of the alveolar lining cells to give rise to tumors is extremely doubtful and denied entirely by some, though Adler[1] considered a case reported by Marchand[59] to be conclusive evidence that growths may occasionally arise from this source. The reader may be referred to Fried's excellent discussion of this phase of the problem. In this connection, one of the most striking cases is that reported by Gray and Cordonnier,[37] who accidently discovered in the course of routine microscopic study three separate minute cancer masses in lungs from the same case. Two of these had the appearance of arising from the epithelium of the ductus alveolaris, while the third resembled an early lymphatic metastasis. Recently, Sweany[87] described in detail a diffuse carcinoma of the lung to which he referred as a "so-called alveolar carcinoma." In this case the author suggested an origin from the epithelium between the lower respiratory bronchioles and the alveoli. Fried,[29d] believing that all growths originate from the bronchial basal or germinal cells, emphasizes the futility of a histogenetic classification.

Histology. On the basis of the foregoing discussion, it is evident that both gross and histogenetic classifications are not completely satisfactory. The only remaining possibility is to classify bronchial carcinoma according to the histologic picture. This has frequently been done and has proved by far the most satisfactory grouping. The multiplicity of cell types has naturally resulted in some confusion and has encouraged somewhat lengthy and often unwieldy classifications. Thus, Shennan[80] recognized six histologic groups with severe subdivisions, and Fried[29d] described five types. Actually it would appear that all carcinomata of the lung could be grouped as either undifferentiated, cylindrical cell, or epidermoid cell.

The true incidence of these various types is difficult to determine. In 23 cases recorded by Boyd,[10] 17 could be classed as undifferentiated (anaplastic 13, medullary 4), 5 as epidermoid and only 1 as cylindrical cell (adenocarcinoma). Simpson,[82] Bonser,[9a,b] Frissell and Knox[31] and others have also found the anaplastic type the commonest. But Weller[94b] found 25 of his cases to be epidermoid, 20 cylindrical and 10 polymorphous, and Brines and Kenning's figures[12] agree with these very closely. On the other hand, Barron,[6] Moise[63] and others have encountered the cylindrical cell growths most frequently. A review of 52 cases in the Department of Pathology of the University of Toronto reveals that undifferentiated growths occurred in 26 instances, cylindrical cell in 15 and epidermoid in 11 cases. The available statistics regarding this problem are not satisfactory for analysis[94b] and inconsistencies such as those above are to be found throughout the literature. This is probably in part due to failure to recognize some of the undifferentiated tumors and in part due to different criteria for classification

being required by different pathologists.[63] Though Fischer-Wassels[27] estimated a quarter of all pulmonary growths were of the undifferentiated type, a general survey led the Reviewer to believe that about 40% of the growths took this form while approximately 30% of the reported cases fell into the cylindrical cell group and 30% into the group of epidermoid tumors.

The class of undifferentiated tumors comprises those anaplastic growths in which it is impossible to determine the type cell giving rise to the tumor. It would include the small spindle and oat-cell growths and probably many of the cases reported as medullary cancer and carcinoma simplex. Typically these tumors are composed of extremely cellular aggregations of small round or spindle-shaped cells with scanty cytoplasm and small, deeply staining nuclei.[5] Ordinarily the stroma is delicate and has a relation to the cell masses characteristic of a carcinoma.[10] Nearly always, if sufficiently diligent search is made, cells can be found differentiating out into either a cylindrical or squamous type and occasionally both may be seen in the same case.[5,82] It is this type of growth which tends to produce the tremendous mediastinal masses and was formerly considered to be other than carcinomatous in nature.[44,82] It is the finding of areas of greater differentiation in this type of tumor which lends weight to the contention that all bronchial growths spring from the germinal or basal layer of the bronchial mucosa, as has been suggested by Fried,[29d] or from cells having a common ancestry.[50]

The cylindrical cell carcinomata of the bronchi do not differ materially from those found elsewhere in the body. The more fully differentiated ones present the typical appearance of an adenocarcinoma, being composed of gland-like structures lined by one or more layers of cuboidal or cylindrical non-ciliated epithelium. Mucous secretion is common and this as well as the histologic resemblance to bronchial mucous glands gave rise to the theory that these tumors actually did originate in these glands. However, the fact that all degrees of undifferentiation are seen in these tumors,[82] the presence of goblet cells in the bronchial lining,[60] and the common parentage of all the respiratory epithelium[50,72] suggest that they might equally well have had their origin from the bronchial mucosa itself. Frequently, adenocarcinomata of the lung show a strong tendency to line the alveoli, using the normal structure as a supporting stroma. This has led some to suggest an alveolar origin for these growths. However, since a similar state of affairs is not uncommonly seen in secondary tumors in the lungs,[50] and since the nature of the alveolar lining cells is still in doubt, it is unsafe to draw any final conclusion.

The epidermoid cell type usually offers little difficulty in recognition, but some pathologists required the formation of pearls and typical intercellular bridges before admitting a case to this class.[63] It would seem more reasonable, however, to admit into this group the less completely differentiated types which resemble epidermoid carcinomata elsewhere in the body. Many of the older pathologists[8,18] and others[53,81] consider these tumors to be either of alveolar origin because of their flattened cells, or else derived from cell rests. Later, it was frequently suggested that they arose from metaplasia of the bronchial epithelium as this condition is not infrequently observed and especially in lungs

which are the seat of a malignant process.[58] Furthermore, it is this type of tumor which tends to occur in relation to chronic inflammatory conditions where metaplasia would be expected to occur. Examples of such tumors are those apparently originating in the walls of tuberculous and bronchiectatic cavities. The similarity in their essential character to the anaplastic tumors is to be seen in the areas of small round and spindle cells also encountered in these growths. Simpson[82] points out that they may give rise to secondaries composed of "oat cells."

It would appear that the most satisfactory grouping is this simple classification based on the microscopic picture which is depicted graphically by Weller[94c] as a Y, the stem representing the anaplastic group. The two arms of the Y represent differentiation toward the epidermoid or cylindrical cell types, the upper extremities of the arms indicating the highest degrees of differentiation. Brines and Kenning,[12] and also Samson[75] have successfully applied this method of grouping, though the former would further simplify it to only two types, differentiated and undifferentiated.

Metastases. The peculiar tendency of bronchial cancers to give rise to widespread metastases has long been recognized. Metastases were recorded in 280 of 374 cases collected by Adler.[1] Fried[29d] observed metastases in all but 3 of his series of 47 cases. Similarly, all who have investigated the problem have been struck with the frequency and wide dissemination of the secondary deposits.

Almost every tissue and organ of the body has been recorded as the site of metastasis, but the highest incidence of extrathoracic deposits is in cervical lymph nodes, liver, abdominal lymph nodes, kidneys, suprarenals, bones, brain, pancreas, and thyroid, in about that order of frequency.[6,9a,12,29d,31,76] Turnbull and Worthington[89] found bronchial growths the commonest source for metastases in bones. The frequency of central nervous system and bone deposits varies widely in different reports, but discrepancies are probably dependent on the extent of the postmortem examinations.

The incidence of metastases to brain is of the greatest interest because of their high frequency and the widely accepted statement that cancer spreads *via* lymphatics. Fried and Buckley[30] were particularly interested in this problem and found 15 central nervous system metastases verified by operation or necropsy in 38 cases studied. They attributed this high incidence to a hematogenous spread and were able in all these cases to demonstrate invasion of blood-vessel walls and lumina by tumor. Boyd[10] cites a similar experience. An analogy has been suggested between brain abscesses secondary to pulmonary suppuration and intracranial tumor deposits secondary to primary bronchial growths. As Fried[30] points out, the situation of the lung in the circulatory system would favor generalized hematogenous dissemination and the formation of metastases in the brain. Tumor emboli from primary sources other than the lungs would tend to be filtered out in these organs and thus fail to reach the brain or indeed the bones and other tissues having no close connection with the primary lesion. Moise[63] had previously suggested a hematogenous spread as the explanation of the widely disseminated metastases.

Although Boyd[10] was unable to demonstrate any correlation between

the tendency of bronchial cancers to metastasize and the cell type or the degree of cell differentiation, Samson[76] arrived at a somewhat different decision in analyzing 100 carefully selected cases. These cases included 34 of his own, the remainder being selected from the literature on the basis of the completeness of the reports. By grouping the tumors as undifferentiated, squamous cell or adenocarcinomata and applying the "coefficient of association" he found the following characteristics: The adenocarcinomata showed a predilection for the central nervous system, adrenals, kidneys, both lungs and to some extent the liver and bones. This was explained on the basis of a hematogenous spread with involvement also of the thoracic and abdominal lymph nodes. The squamous-cell group was largely restricted to local extension with involvement of the bronchial lymph nodes only. The undifferentiated cell type showed extensive lymphogenous spread which was associated with involvement of pancreas, liver and spleen. This is in keeping with the observations of Fried[30] who failed to find any squamous or oat-cell tumors among 15 bronchial carcinomata with central nervous system metastases. The tendency of epidermoid bronchial tumors to extend by local and regional invasion has in the experience of the Reviewer been striking, with the exception of a single case of a well-differentiated epidermoid growth which had given rise to metastases in many organs, including the brain.

These facts have their clinical application, indicating as they do that the squamous-cell tumors offer the best prognosis where surgical intervention is undertaken.[14] Moreover, it must be borne in mind that the presence of central nervous system metastases is apt to lead, in a large number of cases, to an incorrect diagnosis[30] and to subsequent treatment which at the best could be but palliative.

Etiology. Much has been written regarding the etiology of bronchial carcinomata and it is generally concluded that these neoplasms are subject to the same laws as govern the development of carcinomata elsewhere in the body.[82,94b]

Climate and Race. It would appear that climatic conditions have little if any effect on the incidence, though the disease is seen with greater frequency in Great Britain than in continental Europe.[9b] Likewise, racial influences, although they have not been very extensively investigated, are apparently of little significance.[6] However, it does appear that the white races are more susceptible than the colored.[1] Brines and Kenning,[12] at the Receiving Hospital, Detroit, Mich., observed that 50% of their cases were of Central European birth or extraction. Too few studies, however, have been made along these lines to permit any final conclusions.

Age. Cancer of the lung is essentially a disease of middle life. Though cases have been reported at both extremes of age,[24] all authors are agreed that the vast majority occur between the ages of 40 and 70, with the peak in incidence between 50 and 60 years.[9a,26b,82,94b]

Sex. The sex incidence of bronchial cancers is rather striking, since the disease is comparatively uncommon in females. The figures on the male to female ratio vary from 2 to 1 to 4 to 1.[6,9a,26b,29,94b] In a series of cases studied by the Reviewer there were 49 males and only 5 females. A few observers have noted an even more extreme preponderance in males,[10] but the majority of such reports deal with a

comparatively small number of cases. It has been suggested that much of the apparent increase in the disease has been due to its increased incidence among men. Careful analyses, however, such as were carried out by Bonser[96] fail to support this suggestion.

Occupation. This preponderantly male sex incidence has led many to search for some habit or occupation peculiar to the male which might be related to the origin of pulmonary growths.[20] Particular endeavor has been made to establish an occupational linkage.

Brockbank,[13] in a series of 62 cases, found that 14.5% had pursued dusty trades while 29% had been exposed to fumes. Rosedale and McKay[73] found 75% of their cases had been exposed to dusts, and other similar instances are to be found in the literature.[32] In marked contrast with these reports are the figures of Frissell and Knox,[31] who found that only 3 of their 46 cases had been exposed to dusty atmospheres. The vast majority of those who have studied the problem feel that the results of efforts to establish an occupational correlation have, on the whole, been disappointing.[9a,41,68] Sporadic reports of bronchial carcinomata occurring in particular occupations are constantly appearing in the literature, but a summation of these fails to disclose any abnormally altered incidence. An exception to this is to be found in the incidence of the much discussed lung tumors encountered among the miners at Joachimstal[70] and Schneeberg.[77a,b] It is estimated that approximately 50 and 70% respectively of these miners, exposed for a sufficiently long time to the conditions of these mines, eventually die from bronchial carcinoma. The etiology of these tumors will be referred to later.

Naturally the occupations which have been most extensively investigated are those necessitating the inhalation of air contaminated by irritants, either physical or chemical.[4] Much can be learned from the excellent report on the problem by Kennaway and Kennaway,[46] despite the fact that a large portion of their statistical data was obtained from death certificates. These investigators were unable to find any significant occupational incidence but observed that the highest incidence occurred among open air workers exposed to road dusts, with the exception of motor vehicle operators. Metal grinders and those exposed to coal gas, tar and tobacco dusts also showed a slightly greater incidence of lung cancers than the general population. Others, including Simpson,[82] have also noted a high incidence among open air workers, but Bonser[96] was unable to support this finding, since the majority of her cases were indoor workers.

The observation has often been made that cancer of the lung is primarily a disease of the laboring classes.[13] Though this may be true, the statement should be accepted only with reserve, since the majority of patients admitted to most of the large hospitals and institutions are of the laboring class, while the well-to-do patronize private hospitals and fail to come to autopsy.

Chronic Irritation. Approaching the problem from a different point of view, many investigators have made an equally exhaustive search for specific causes of bronchogenic cancers. Though none has been satisfactorily proven, it now appears highly probably that chronic irritation of the respiratory tract is of the greatest possible significance.[12] The irritants that have been incriminated include gross acute trauma, bacterial, physical and chemical agents.

Trauma. This is in all likelihood of no significance.[1,52] Reports of cases of bronchial carcinoma apparently developing after an injury to the chest are scattered throughout the literature, but the majority are inconclusive. The most convincing is that recorded by Wells and Cannon.[96] In this particular case, the injury was immediately followed by the development of subcutaneous emphysema and hemoptysis, indicating that damage to the pulmonary tissues had occurred. Roentgen ray and physical examination revealed no neoplasm at that time. Two years after the accident, death occurred from a primary pulmonary cancer situated peripherally in the lung immediately beneath the site of the injury. It is, of course, impossible, as Wells himself admits, to prove that a minute neoplasm did not exist prior to the occurrence of the trauma.

Infections. As regards the relation of bacterial infections to carcinoma of the lung, attention in recent years has centered largely in the possible influence of influenza. This was probably stimulated by the apparent increase in bronchial growths observed by some workers as corresponding with and following the epidemic of 1918–1920.[6,63] Peculiar lesions suggesting precancerous changes have long been recognized as occurring in the lungs in association with inflammatory conditions.[38] These changes, following influenza, were well described by Winternitz in 1920.[99] They took the form of active epithelial proliferations which often advanced to such an extent as to resemble "an infiltrating malignant epithelial neoplasm." Winternitz[98] also observed very similar changes in the lungs of rabbits following the insufflation of dilute hydrochloric acid. Askanazy[3] observed that squamous metaplasia in the bronchi was common in individuals dying from influenza. Clinical studies have failed, however, to show any convincing relationship between influenza and bronchial tumors.[29d,47,82] Many writers have observed that the peak in the alleged increasing incidence of bronchial cancer was reached prior to 1918, and no undue increase in the incidence of the condition was recorded following the influenza epidemic of 1894.[42,94b] Furthermore, relatively few patients suffering from carcinoma of the lung give an antecedent history of influenza, and doubt has also been expressed as to the ability of a single acute infection to initiate changes leading to the development of cancer.[29d]

Among the chronic infective pulmonary lesions, tuberculosis has been accused most frequently of being one of the causative factors responsible for bronchial carcinoma. Cancer of the skin following lupus vulgaris is frequently pointed to as an analogous example.[23a,65] Ewing,[24] in 1928, stated that tuberculosis was the chief etiologic factor, basing his conclusions on the apparently frequent coëxistence of the lesions as reported by some authors. Barron[6] also considered tuberculosis as an important factor. Actually, tuberculosis is encountered not infrequently in association with bronchial growths, but it is doubtful if the association of tuberculosis is any commoner with carcinoma of the lung than with other diseases. Usually there is no evidence of anatomic relationship between the two processes and more often than not the tuberculous lesions are entirely inactive. In 139 cases studied by Simpson[82] evidence of tuberculosis was found in only 47. In 6 of these the tuberculous process was active; in 7, healed nodules were found in the lungs; and in 34 there were only calcareous hilar and mediastinal

glands. Frissell and Knox[31] observed tuberculous lesions in only 18.6% of their cases, while Sison and Monserrat,[83] in the Philippines, noted that the incidence of lung cancer was low while that of tuberculosis was high. Fried[29d] found a lower incidence of malignancy among a group of tuberculous cases than in a similar group of non-tuberculous individuals. Similar experiences have been reported by Lubarsch,[56] while Lóizaga and Vivoli[55] encountered but 1 carcinoma of the lung in 2400 autopsies on tuberculous patients. Fishberg[26a] suggests that the presence of a pulmonary neoplasm may by pressure activate an old tuberculous focus, but considers the association of the two conditions uncommon. Fried[29e] has recently reported a series of 13 cases in which the lesions coëxisted. While tuberculosis cannot be considered a common etiologic factor, it would seem reasonable to agree that those carcinomata reported as arising in tuberculous cavities are probably the result of the chronic inflammatory changes and consequent metaplasia, but this does not imply any carcinogenic effect on the part of the tubercle bacillus itself.

Non-specific chronic inflammatory lesions of the lungs would appear to be of considerable importance as a predisposing factor. Thus squamous-cell growths arising in bronchiectatic cavities are not rare. Marron[6] suggests that the bronchiectasis is more likely the result rather than the cause of the growth. Though this is certainly often true, it is not always so. The Reviewer has observed 1 case in which the tumor formed the walls of a bronchiectatic cavity in an individual who had suffered from bilateral bronchiectasis for at least 15 years. Frequently, it is possible to elicit a history of chronic bronchitis, recurring attacks of pneumonia or other low-grade inflammatory pulmonary condition in patients suffering from a bronchial growth.[29d,43,82] It is even commoner to find gross and microscopic evidence of chronic pulmonary inflammation at autopsy.[50,63] Caution, of course, must be exercised in expressing an opinion as to whether or not these chronic inflammatory changes antedated the development of the neoplasm. Gray and Cordonnier's case[37] is an excellent example of an extremely early growth in a chronically diseased lung. These chronic and apparently non-specific conditions are frequently the sequelæ to previous acute events and probably of greater significance than the original acute irritation.[50]

The relationship between chronic inflammation of the lungs and carcinoma is probably dependent upon injury to the epithelial elements with regeneration and often metaplasia. That metaplasia does occur in association with many conditions, including tuberculosis, bronchiectasis, fibrosing pneumonias, collapse of the lung and chronic bronchitis has frequently been pointed out.[29d,50,94b] Geschickter and Denison[35] and von Glahn[91] noted that squamous-cell tumors of the lung were commoner in the upper age group and it is in the aged that metaplastic changes are most often observed.[50] The bronchiectasis with metaplasia which has frequently been observed in laboratory rats and on occasion erroneously described as a squamous-cell tumor cannot be considered comparable to the disease in man, since it has a totally different etiologic background.[69]

Syphilis of the lung has occasionally been recorded as being associated with bronchial cancer[82] but is rare and probably bears no causal relationship other than that of a chronic irritant. Even rarer is the asso-

ciation of pulmonary cancer and parasites, even those parasites notorious for their ability to initiate neoplastic lesions elsewhere.[29d] Eggers[23] quotes 1 case reported by Babes of bronchogenic cancer associated with trichinosis.

Chemical and Physical Agents. The alleged increase in the incidence of lung tumors has resulted in an analysis of the habits of modern civilization in the hope of discovering some predisposing factors. Thus, smoking of tobacco, exposure to dust from tarred roads and the inhalation of fumes from gasoline engines have all been incriminated. McNally[61] suggested that nicotine, phenol bodies, pyridine bases and ammonia, contained in cigarette smoke, were irritants which could account for "cigarette cough," chronic bronchitis, leukoplakia and the recorded increase in cancer of the lung. Hoffman,[40] on the basis of elaborate and confusing statistics, concluded that smoking habits unquestionably increase the liability to cancer of the mouth, esophagus, larynx and the lungs. Hoffman adds the astounding statement that non-smokers are subjected to the same dangers owing to air pollution by smokers. However, it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank[13] found but 14.5% of his cases heavy smokers, while 21% were non-smokers. Furthermore, if smoking were a factor of any importance it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women.[94b]

The development of tarred roads led to much speculation as to a possible etiologic relationship. Some weight is lent to this idea by such observations as those of Kennaway and Kennaway,[46] who noted an increased incidence of cancer of the lung among open air workers exposed to road dusts. It seems remarkable, however, that this observation did not apply to motor vehicle operators who surely suffer a similar exposure. Though a high incidence of lung tumors has been reported from regions where road tarring is not practised,[10] Campbell[15] does not consider this an argument against an etiologic relationship, stating that dust from such roads may be carried tremendous distances by the air currents. This cannot, however, be considered tenable in view of reports from communities[10] where the injurious agents would have to be carried hundreds or even thousands of miles. Campbell[15] found a high incidence of warts which underwent malignant changes in laboratory animals exposed to dusts from tarred roads, but no pulmonary neoplasms developed. Passey and Holmes,[68] carefully analyzing the problem, point out that the alleged increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further suggest that if the time factor required to produce growths in animals, as demonstrated by Campbell, were applied to man, the effect of road tarring should just now be making itself felt.

Fumes from gasoline engines and pollution of the air in industrial centers[19,79] can be considered under the same category of etiologic agents as dusts from tarred roads. There is certainly no direct evidence to connect lung cancers with the first of these. Though a high incidence of carcinoma of the lung has been noted in some industrial centers where air pollution was great, an equally high incidence has

been observed in rural communities.[10] It has also been noted that there is no undue occurrence of the disease among mechanics and garage workers who are constantly exposed to a polluted atmosphere.[68] Although Kimura,[48] in 1923, reported an adenoma of the lung in a rabbit and an adenocarcinoma of the lung in a guinea-pig following the insufflation of coal tar, Smith,[85] in 1928, was unable to produce pulmonary tumors in mice by exposing the animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline. Although Smith thus found nothing to support the theory that fumes from coal tar or gasoline were of importance in human cases of bronchial cancer, reports such as that of Kawahata[45] are most suggestive. This investigator observed 12 cases of the disease among employees tending furnaces for gas production, where the air contained several tar derivatives with unknown carcinogenic properties. Recently, Seelig and Benignus[79] found 8 adenocarcinomata of the lung in 100 mice exposed to coal soot, while only 1 tumor developed in their controls. It must be concluded, however, that the evidence incriminating inhaled tar products as a cause of cancer of the lung in human beings is as yet far from convincing.

The peculiarly high incidence of bronchial cancers seen among the miners at Schneeberg and Joachimstal, and previously referred to, has also led to speculation regarding the possible presence of a specific agent in the mine dusts. The dusts of both mines are radioactive and, in addition, contain bismuth, cobalt, nickel and arsenic. Analysis of lungs obtained at autopsy from miners at both these sources have proved entirely negative as to radioactivity and any significant chemical content. As pointed out by Pirchan,[70] these negative results do not rule out the possibility of a chemical factor, no trace remaining owing to its rapid removal. Arsenic has been suspected because of its known carcinogenic effects upon skin.[50] Schmorl[77a] was impressed by the constant and marked pneumoconiosis found in association with the growths at Schneeberg, and he originally believed that physical irritation was the probable cause of the tumors. Later, he suggested that the radioactivity as well as the arsenic content of the dust might be additional factors.[77b] Mice exposed to the mine dusts showed only negative results.[74] The Schneeberg mines are described as damp, infested with a variety of moulds and conducive to the development of chronic bronchial catarrh[77b] which in itself might be of some importance. At Joachimstal, pneumoconiosis was not a prominent feature, as shown by Pirchan,[70] but the lungs of miners dying with pulmonary growths presented a picture otherwise morphologically identical with that described by Schmorl. Pirchan was inclined to consider the radioactivity of the mine dusts and air as the most probable specific agent. It is said that the incidence of carcinoma of the lung is decreasing at Schneeberg following the introduction of respirators,[29d] which suggests that the factors responsible for the pneumoconiosis are also related to the production of the growths. On the other hand, respirators have been used at Joachimstal and the incidence of tumors remains high, while pneumoconiosis is uncommon.[70] This problem, though fascinating, is confusing in the extreme and can by no means be considered settled.

Silica has frequently been considered as a possible etiologic agent and

a number of cases of silicosis associated with carcinoma of the lung have been reported. However, it has been pointed out by Simpson[82] and Passey,[68] and more recently, by Vorwald and Karr,[92] that cancer of the lung is rare among South African gold miners, while silicosis is common. Indeed, the latter investigators found a slightly diminished incidence of the disease among silicotics as compared with the population at large. This failure to show an increased incidence is in accord with the earlier observations of Pancoast and Pendergrass,[67] Allen[2] and others. However, numerous cases where silicosis and cancer of the lung have coexisted are now to be found in the literature.[17,22,25,32,36a,b,57,66] Dible[17] and others believe there may be a direct relationship. Willis and Brutsaert[97] observed tumor-like structures surrounding the bronchi of several guinea-pigs from a series of animals exposed to silica for long periods of time. They concluded that these lesions were in all probability a hyperplastic response to the irritating silica. The Reviewer[49] reported recently an extremely high incidence of bronchogenic carcinoma in a small series of silicotics numbering 50, 9% of which showed primary epithelial malignancies of the lungs in addition to the lesions resulting from prolonged exposure to silica. It was, therefore, suggested that silica might in certain cases be a specific predisposing factor.

Ewing[24] suggested that pulmonary carcinoma might possibly arise from bronchial papillomata. This must indeed be rare as the incidence of benign epithelial bronchial growths is exceedingly low. In reviewing the literature up to 1935, reports of only 58 benign bronchial growths of all types were encountered, and only 18 of these were sufficiently well described to be classed as epithelial. The remainder was composed of tumors referred to as polypi, granulomata, chrondromata, lipomata and so forth.

Heredity. A discussion on the etiology of cancer of the lung would not be complete without reference to hereditary factors which may prove to be of extreme importance. Though no hereditary factor has ever been satisfactorily demonstrated in carcinoma of the human lung,[6] Slye[84] and others find an extremely strong hereditary predisposition in mice. By careful breeding, it is possible, as has been frequently demonstrated, to develop cancerous and non-cancerous strains. On the basis of such studies as have been made on tumors in identical twins, Lockhart-Mummery[54] concludes that the "intrinsic factor of hereditary susceptibility to tumour formation in human beings is of far greater importance than the extrinsic or environmental factor." Fischer-Wassels[27] also apparently believes this to be of considerable importance in relation to cancer of the lung in man, and suggests that the probable sequence of events in the development of such a tumor is hereditary predisposition, irritation, repair with excessive proliferation and finally malignancy, and one finds it difficult not to agree.

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REFERENCES.

(1.) **Adler, I.**: Primary Malignant Growths of the Lungs and Bronchi, New York, Longmans, Green & Co., 1912. (2.) **Allen, M. L.**: J. Indust. Hyg., **16**, 346, 1934. (3.) **Askanazy, J.**: Cor.-Bl. f. schweiz. Aerzte, **49**, 465, 1919. (4.) **Bainbridge, W. S.**: Internat. J. Med. and Surg., **46**, 421, 1933. (5.) **Barnard, W. G.**: J. Path. and Bact., **29**, 241, 1926. (6.) **Barron, M.**: Arch. Surg., **4**, 624, 1922. (7.) **Bayle, G. L.**: Recherches sur la phthisie pulmonaire, Paris, Gabon, 1810. (Quoted by

Hruby,[41] Weller,[94a] Adler,[1] and others.) (8.) **Beitzke, H.**: Atmungsorgane, in Aschoff: Pathologische Anatomie, Jena, G. Fischer, **2**, 255, 1923. (Quoted by Fried.[28d]) (9.) **Bonser, G. M.**: (*a*) J. Hyg., **28**, 341, 1929; (*b*) Ibid., **34**, 218, 1934. (10.) **Boyd, W.**: Canad. Med. Assn. J., **23**, 210, 1930. (11.) **Breckwoldt, R.**: Ztschr. f. Krebsforsch., **23**, 128, 1926. (Quoted by Bonser.[9a, b]) (12.) **Brines, O. A.**, and **Kenning, J. C.**: Am. J. Clin. Path., **7**, 120, 1937. (13.) **Brockbank, W.**: Quart. J. Med., n.s., **1**, 32, 1932. (14.) **Brunn, H.**: Arch. Surg., **12**, 406, 1926. (15.) **Campbell, J. A.**: Lancet, **1**, 233, 1934. (16.) **Davidson, M.**: Ibid., **2**, 1181, 1929. (17.) **Dible, J. H.**: Ibid., **2**, 982, 1934. (18.) **Dömeny, P.**: Ztschr. f. Heilk., **23**, 407, 1902. (Quoted by Moise.[63]) (19.) **Duguid, J. B.**: Lancet, **2**, 111, 1927. (20.) Editorial: Ibid., **2**, 125, 1927. (21.) **Edwards, T. E.**, and **Taylor, A. B.**: Brit. J. Surg., **25**, 487, 1938. (22.) **Egbert, D. S.**, and **Geiger, A. J.**: Am. Rev. Tuberc., **34**, 143, 1936. (23.) **Eggers, H. E.**: Arch. Path., **12**, 983, 1931. (24.) **Ewing, J.**: Neoplastic Diseases, 3d ed., Philadelphia, W. B. Saunders Company, 1928. (25.) **Fine, M. J.**, and **Jaso, J. V.**: J. Am. Med. Assn., **104**, 40, 1935. (26.) **Fishberg, M.**: (*a*) Pulmonary Tuberculosis, 3d ed., Philadelphia, Lea & Febiger, 1922; (*b*) Arch. Int. Med., **37**, 745, 1926. (27.) **Fischer-Wassels, B.**: Frankf. Ztschr. f. Path., **49**, 145, 1936. (28.) **Fremont-Smith, M.**, **Lerman, J.**, and **Rosahn, P. D.**: New England J. Med., **203**, 473, 1930. (29.) **Fried, B. M.**: (*a*) Arch. Int. Med., **35**, 1, 1925; (*b*) Arch. Path., **3**, 751, 1927; (*c*) Arch. Int. Med., **40**, 340, 1927; (*d*) Medicine, **10**, 373, 1931; (*e*) Am. J. Cancer, **23**, 247, 1935. (30.) **Fried, B. M.**, and **Buckley, R. C.**: Arch. Path., **9**, 483, 1930. (31.) **Frissell, L. F.**, and **Knox, L. C.**: Am. J. Cancer, **30**, 219, 1937. (32.) **Frommel, E.**: Rev. de méd., Paris, **44**, 31, 1927.

(33.) **Gazayerli, M. E.**: J. Path. and Bact., **43**, 357, 1936. (34.) **Gazayerli, M. E.**: J. Hyg., **36**, 449, 1936. (35.) **Geschickter, C. F.**, and **Denison, R.**: Am. J. Cancer, **22**, 854, 1934. (36.) **Gloyne, R. S.**: (*a*) Tubercle, **17**, 5, 1935; (*b*) Ibid., **18**, 100, 1936. (37.) **Gray, S. H.**, and **Cordonnier, J.**: Arch. Surg., **19**, 1618, 1929. (38.) **Haythorn, S. R.**: J. Med. Res., n.s., **21**, 523, 1912. (39.) **Henrici, A. T.**: Ibid., **26**, 395, 1912. (40.) **Hoffman, F. L.**: Ann. Surg., **93**, 50, 1931. (41.) **Hruby, A. J.**, and **Sweany, H. C.**: Arch. Int. Med., **52**, 497, 1933. (42.) **Hueper, W.**: Am. J. Path., **2**, 81, 1926. (43.) **Hunt, T. C.**: Lancet, **1**, 759, 1929. (44.) **Karsner, H. T.**, and **Saphir, O.**: Am. J. Path., **6**, 533, 1930. (45.) **Kawahata, K.**: Gann, **30**, 341, 1936. (46.) **Kennaway, M. N.**, and **Kennaway, E. L.**: J. Hyg., **36**, 236, 1936. (47.) **Kikuth, W.**: Virchow's Arch. f. path. Anat., **255**, 107, 1925. (48.) **Kimura, N.**: Japan. Med. World, **3**, 45, 1923. (49.) **Klotz, M. O.**: Am. J. Cancer. (50.) **Klotz, O.**: Canad. Med. Assn. J., **27**, 989, 1927. (51.) **Klotz, O.**, and **Simpson, W.**: Libman Anniv. Vols., **2**, 685, 1932. (52.) **Knox, L. C.**: Arch. Path., **7**, 274, 1929. (53.) **Lilienthal, H.**: Arch. Surg., **8**, 308, 1924. (54.) **Lockhart-Mummery, J. P.**: Lancet, **1**, 155, 1934. (55.) **Lóizaga, N. S.**, and **Vivoli, D.**: Semana méd., **1**, 2022, 1934. (56.) **Lubarsch**: Cancer et tuberculose, Actualité médicale, 1901. (Quoted by Fried.[28a]) (57.) **Lynch, K. M.**, and **Smith, W. A.**: Am. J. Cancer, **24**, 56, 1935. (58.) **Maclachlan, W. W.**: Atlantic Med. J., **26**, 655, 1923. (59.) **Machand**: Quoted by Adler.[1] (60.) **Maximow, A. A.**, and **Bloom, W.**: A Text-Book on Histology, Philadelphia, W. B. Saunders Company, 1930. (61.) **McNally, W. D.**: Am. J. Cancer, **16**, 1503, 1932. (62.) **Mills, R. G.**, and **Mumey, N.**: Arch. Int. Med., **43**, 516, 1929. (63.) **Moise, T. S.**: Ibid., **28**, 733, 1921. (64.) **Morgagni, G. B.**: De Sedibus et Causis Morborum per anatomen indigatis, 1761, lib. II ep. 20 art. 39 and ep. 22 art. 22. (Quoted by Weller[94b] and others.) (65.) **Oertel, H.**: J. Med. Res., **20**, 503, 1912. (66.) **Olson, K. B.**: Am. J. Path., **2**, 449, 1935. (67.) **Pancoast, H. K.**, and **Pendergrass, E. P.**: J. Am. Med. Assn., **101**, 587, 1933. (68.) **Passey, R. D.**, and **Holmes, J. M.**: Quart. J. Med., n.s., **4**, 321, 1935. (69.) **Passey, R. D.**, **Leese, A.**, and **Knox, J. C.**: J. Path. and Bact., **42**, 425, 1936.

(70.) **Pirchan, A.**, and **Sikl, H.**: Am. J. Cancer, **16**, 681, 1932. (71.) **Rolleston, H. D.**, and **Trevor, R. S.**: Brit. Med. J., **1**, 361, 1903. (72.) **Rosahn, P. D.**: Am. J. Med. Sci., **179**, 803, 1930. (73.) **Rosedale, R. S.**, and **McKay, D. R.**: Am. J. Cancer, **26**, 493, 1936. (74.) **Rostoski, O.**: Report of the Intern'l Conf. on Cancer, London, July 17–20, 1928, Bristol, John Wright & Sons, 1928. (75.) **Samson, P. C.**: Am. J. Cancer, **23**, 741, 1935. (76.) **Samson, P. C.**: Ibid., p. 754. (77.) **Schmorl, G.**: (*a*) Centralbl. f. allg. Path. u. path. Anat., **33**, 577, 1922; (*b*) Report of the Intern'l Conf. on Cancer, London, July 17–20, 1928, Bristol, John Wright & Sons, 1928. (78.) **Scott, E.**, and **Forman, J.**: Med. Rec., **90**, 452, 1916. (79.) **Seelig, M. G.**, and **Benignus, E. L.**: Am. J. Cancer, **28**, 96, 1936. (80.) **Shennan, T.**: J. Path. and Bact., **31**, 365, 1928. (81.) **Siegert, F.**: Virchow's Arch. f. path. Anat., **129**, 413, 1892. (82.) **Simpson, S. L.**: Quart. J. Med., **22**, 413, 1929. (83.) **Sison,**

A. G., and **Monserrat, C.**: J. Philippine Islands Med. Assn., **7**, 422, 1927. (Quoted by Von Glahn.[91]) (**84.**) **Slye, M., Holmes, H. F.**, and **Wells, H. G.**: J. Med. Res., **30**, 417, 1914. (**85.**) **Smith, R. E.**: J. Cancer Res., **12**, 134, 1928. (**86.**) **Stevens, A. A.**: Paper read before the College of Physicians of Philadelphia, March 25, 1912. (**87.**) **Sweany, H. C.**: Arch. Path., **19**, 203, 1935. (**88.**) **Thomas, B. A.**: J. Am. Med. Assn., **86**, 1957, 1926. (**89.**) **Turnbull, H. M.**, and **Worthington, R.**: Arch. Path. Inst. London Hosp., **2**, 163, 1908. (**90.**) **Vinson, P. D.**: J. Am. Med. Assn., **107**, 258, 1936. (**91.**) **Von Glahn, W. C.**: Am. Rev. Tuberc., **21**, 57, 1930. (**92.**) **Vorwald, A. J.**, and **Karr, J. W.**: Am. J. Path., **14**, 49, 1938. (**93.**) **Wahl, S.**: Ztschr. f. Krebsforsch., **25**, 302, 1927. (Quoted by Bonser.[93]) (**94.**) **Weller, C. V.**: (*a*) Arch. Int. Med., **11**, 314, 1913; (*b*) Arch. Path., **7**, 478, 1929; (*c*) J. Cancer Res., **13**, 218, 1929. (**95.**) **Wells, H. G.**: J. Am. Med. Assn., **88**, 399, 476, 1927. (**96.**) **Wells, H. G.**, and **Cannon, P. R.**: Arch. Path., **9**, 869, 1930. (**97.**) **Willis, H. S.**, and **Brutsaert, P.**: Am. Rev. Tuberc., **17**, 268, 1928. (**98.**) **Winternitz, M. C., Smith, G. H.**, and **McNamara, F. P.**: J. Exp. Med., **32**, 205, 1920. (**99.**) **Winternitz, M. C., Wason, J. M.**, and **McNamara, F. P.**: The Pathology of Influenza, New Haven, Yale University Press, 1920.

HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

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CHANGING CONCEPTIONS OF SCARLET FEVER.

Severity. Pope,[22] in 1926, using Chapin's material, reviewed the experience of Providence, R. I., in regard to scarlet fever in the years from 1865 to 1924. The death rate for children of ages from 2 to 4 had decreased in this interval from 691 to 28 per 100,000 (or to about 1/25 of the rate of 70 years ago) but the attack rate had not presented a corresponding decrease. The decrease in the number of deaths could not be attributed to a lower average prevalence nor to any changes in the population, but must have been due to the lessened severity of the disease. In 1886–88, 1 in every 5 cases died, while in 1923–24, only 1 of every 114 cases ended fatally.

In a recent (1933) publication, Woods[31] has shown that a similar change has occurred in England and Wales. While the population of children exposed to risk has increased some 40%, the deaths from scarlet fever *are less than 1/25* of the absolute number recorded 80 years ago. In the face of this decrease in the death toll, the disease has not diminished generally in prevalence. The decrease in the number of fatalities is due to the lessened severity of the disease.

These observations could be amplified and corroborated by a review of other reports, but the general facts are well established and appreciated. Although the decrease in the case fatality rate has been more rapid in some areas than in others, perhaps more marked in southern than in northern climes, and more apparent during endemic than during epidemic prevalence, it has become general throughout Europe and America. From a fearful and highly fatal malady scarlet fever has become a relatively mild and, in the vast majority of instances, an innocuous ailment.

That it will continue to exhibit its present mild character is open to question. To Thomas Sydenham, "febris scarletina" was a mild disease. By the end of the eighteenth century, a severe form was prevalent in England, for in Willan's reports on diseases in London in the years from 1796 to 1800, there are numerous references to the gravity of the scarlet fever at that time. Immediately after this period, the severity diminished. Bateman, writing of the disease of London in years from 1804 to 1816, frequently alludes to the mild type of scarlet fever. There is no question that a change occurred after 1830 and the disease became, as Creighton noted, "the leading cause of death among the infectious diseases of childhood." Apparently it remained so in England and in this country until the middle of the nineteenth century, when the decline in mortality that has been noted began and has continued to the present time. This history is a warning against optimism until the causes of the decrease can be defined and explained.

Pathogenesis. With the advent of the bacteriologic era it was confidently expected that the disease "scarlet fever" would be found to be due to a specific microbial incitant, just as were diphtheria, typhoid, tuberculosis and other common infectious disease. After 50 years of research, the true nature of the pathogenesis of the disease syndrome has finally become apparent.

The etiologic relationship of streptococci was suspected very early, but attempts to separate those types which were capable of causing scarlet fever from those which were not, by means of cultural and serologic procedure, were only partially successful. It became evident that they belonged to the "hemolytic" streptococci and that they possessed some degree of antigenic relationship. The nature of the essential biologic activity which distinguished them remained undiscovered until some 15 years ago.

At this time, as a result of the observations and experiments of Schultz and Charlton, Mair, Dochez, and the Dicks, it became evident that the peculiar biologic activity which distinguished the hemolytic streptococci which caused scarlet fever was their ability to produce a particular toxin, called Dick toxin, or, more properly, erythrogenic toxin, erythrotoxin, or simply rash-producing toxin. It was demonstrated that the injection of bacteria-free filtrates of broth cultures of hemolytic streptococci containing this erythrotoxin into susceptible human beings reproduced cardinal symptoms of scarlet fever, except the sore throat; namely, fever, malaise, nausea, vomiting, and a generalized scarlet rash. This afforded a rational interpretation of the pathogenesis. The sore throat is due to the primary localization of a strain of hemolytic streptococci in the throat with the resulting inflammatory reaction. The characteristic constitutional reaction is due to the toxic products peculiar to these organisms. The complications and ultimate outcome are determined by the ability of the organism to proliferate locally and to invade the tissues progressively. Resistance and recovery depend upon the development of at least two types of immunity: (*a*) ability to prevent the growth and progressive invasion of the microörganism, that is, antibacterial; and (*b*) ability to neutralize the toxic products, especially the erythrotoxin, that is, antitoxic immunity. To what extent the latter affects the former is not yet clear.

This conception of the pathogenesis of scarlet fever has now received general acceptance. It raises a pertinent question: Should scarlet fever be regarded as a separate and distinct disease or simply as one of the clinical patterns or syndromes resulting from infection with hemolytic streptococci? The answer will depend very largely on whether it can be demonstrated that hemolytic streptococci which cause scarlet fever form a separate and distinct group meriting some such appellation as "Strep. hemolyticus var. scarlatinæ" or equivalent.

Identification of Scarlet Fever Streptococci. The question of the specificity of the scarlet fever streptococci is but a small part of the larger problem of the classification of streptococci in general and the correlation of types or subdivisions with the various conditions of health and disease in which they are found in man and animals. The present (1937) status of knowledge has been admirably reviewed by Sherman.[23] Attention here will be limited to those streptococci which produce characteristic beta-type hemolysis in blood agar.

In the previous discussion, it was pointed out that the significant biologic activity which distinguished the hemolytic streptococci recovered from cases of scarlet fever was their ability to produce, under specified conditions of culture, the characteristic erythrotoxin. Effort has been made to use this quality as a means of identification. It has become evident, however (Kirkbride and Wheeler,[15] Eagles,[7b] Smith,[24b] McLachlan,[20a] *et al.*), that the ability to produce erythrotoxin is a function not peculiar to strains of hemolytic streptococci from scarlet fever alone, but possessed not infrequently by non-scarlatinal strains. Neither on the basis of the quality nor quantity of erythrotoxin produced can a sharp distinction be made.

Researches upon the serologic identification of hemolytic streptococci, although discouraging for a long time, recently have been proved to be of considerable value. It will be recalled that up to 1930 there were two schools of thought. From the work of one group, Dochez, Avery and Lancefield,[6] Bliss,[3] Eagles,[7a] Gordon,[9] *et al.*, it appeared that most strains of hemolytic streptococci—if not all—which caused scarlet fever, could be identified by three or four properly prepared type-agglutinating sera, and that they formed a group serologically distinct from non-scarlatinal strains. To the other group, working more recently, Griffith,[11] Smith,[24a] James,[14] and McLachlan and Mackie,[21] it seemed that the situation was not so simple. Although certain predominant serologic types could be demonstrated along scarlatinal strains, similar types could be recovered from non-scarlatinal sources. Summarizing in 1932, the late Sir Frederick Andrewes[2] concluded that no one serologic form can be credited with the causation of scarlet fever, though three or four recognizable serologic types, namely, Griffith's four major types, I, II, III and IV, seemed to be exceptionally commonly found in cases of the disease. To him it seemed that "the more one studies hemolytic streptococci the more strongly is the impression gained that they are in a state of constant flux in which it is difficult to find any firm foundation for a permanent systematic classification."

However, even while these pessimistic views were being written, the researches of Lancefield[16] upon the antigenic composition of the streptococci were paving the way for the firm foundation of which Andrewes speaks. By means of a precipitin reaction, based upon the presence in

these organisms of a group specific polysaccharide, the "C" substance, it was found that the hemolytic streptococci could be divided into broad serologic groups which correlated significantly with previous knowledge of host relationships and pathogenicity. In particular, nearly all of the strains of hemolytic streptococci which are important in human pathology, fall into one group: Lancefield's Group A (Swift, Lancefield and Goodner,[27] Hare,[12] Davis and Guzdar,[5] Lancefield and Hare,[17] Hare and Maxtell,[13] Colebrook, Maxtell and Johns[4]).

Having established this broad group, it is possible to subdivide it into types by means of a precipitin test based upon extracts of the type-specific protein, the "M" substance contained in streptococci, or by means of agglutination. Independently, Griffith,[11b] by means of a slide agglutination, had established 27 types of Strep. pyogenes and stated that more than 30 such types exist. All but two or three of Griffith's types have been found to belong in Lancefield's Group A. There was thus afforded the basis for the serologic identification of the principal pathogenic hemolytic streptococci and their subdivision into types.

On the basis of experience up to the present time, certain types, 1, 2, 3, 4, 8, 10 (N. Y. 5), 11, 12, 23, have been found fairly commonly in scarlet fever; Types 5, 6, 13, 15, 19, 22, 26 and 27, less often. It is equally notable that these same types, and those remaining, have been found in non-scarlatinal conditions, such as tonsillitis, septic sore throat, otitis, mastoiditis, septicemia, puerperal sepsis, erysipelas, as well as occasionally upon normal human skin and mucous membranes. In other words, *by serologic technique the types of hemolytic streptococci which cause scarlet fever can be identified, but they cannot, by this means alone, be differentiated sharply from the other types in Lancefield's Group A which have been recovered from non-scarlatinal conditions.*

Production and Purification of Erythrotoxin and the Dick Reaction. One of the most valuable contributions of the Dicks was the development of the skin test which bears their name. It is not intended to review here the extensive literature which has appeared supporting the view that the principal hypothesis upon which the test rests is correct. Experience has shown that anomalies occur as with other similar tests (McGibbon,[19] Fraser[8a]) and certain limitations to interpretation which were not at first appreciated have become apparent.

Two important sources of error have been demonstrated: (*a*) the confusion caused by allergic reactions to other constituents of the test material, and (*b*) qualitative differences in the erythrotoxin produced by some strains of streptococci.

Although there has been some difference of opinion as to the frequency of "pseudo-reactions" due to allergy, and the necessity, therefore, for a simultaneous control test, recent work has emphasized that this source of error cannot be ignored.

As a result of the researches of Ando, Kurauchi and Nishimura,[1] Toyoda and Fugati,[28] Green,[10] and Veldee,[30] it has been found that crude filtrates produced according to the Dick method contain at least two substances capable of invoking skin reactions: (*a*) The first is contained in an alcohol-insoluble fraction. It is heat-labile, that is, completely inactivated by heating for 30 minutes at 100° C. It invokes the Dick test reaction of susceptibility, combines readily with antitoxin and produces the symptoms of scarlet fever (except sore throat) when

injected in a sufficiently large dose in a Dick-positive child. This fraction evidently contains, in a considerable degree of purity, the essential erythrogenic toxin. (*b*) The second fraction is both alcohol- and acetic acid-insoluble. It is heat-stable, that is, boiling for 3 hours is required to destroy it. It possesses no combining power with antitoxin. It produced both local and constitutional reactions (but which are not typical of scarlet fever) when injected in sufficiently large doses, particularly in an adult. It is apparently identical with the nucleoprotein obtained by the extraction of the washed bacteria themselves, and the skin reaction resulting from the injection of this fraction is a manifestation of sensitization to this bacterial protein without relation to susceptibility to scarlet fever.

Veldee[30] (1937) notes that the coëxistence of these two fractions in the crude toxin should cause no surprise in view of our more extensive knowledge of the reactions induced by diphtheria toxin where an exactly parallel situation exists. Susceptibility to the true toxins in either disease occurs when the circulating antitoxin falls sufficiently low; whereas reaction to the heat-stable bacterial protein is dependent upon sensitization to this protein brought about by actual contact with specific protein. Hence we find that disease susceptibility (as measured by the Dick or Schick tests) decreases with age and extent of exposure; whereas sensitivity to nucleoprotein increases with age and extent of exposure. Not infrequently, reaction to both factors exists in the same individual.

Concerning the second source of error, although the erythrotoxin produced by most strains of scarlet fever streptococci is essentially similar, some degree of heterogeneity exists (Trask and Blake[29]). To cover the range of variation, the Dicks require that the pooled products of four selected strains be used in the manufacture of toxin and antitoxin. The scarlet fever antitoxin in routine use produced under the Dick patents neutralizes the toxins used in the Dick test, but fails to neutralize the toxins of about 10% of the strains isolated from patients (Fraser[8a]). When exposure to such strains occurs, one might expect even a Dick-negative person to develop scarlet fever.

With these qualifications, *the Dick test is a reliable indication of the level of "anti-erythrotoxin"* in the individual's tissues. It has not yet been proved, however, that a negative Dick test necessarily implies an ability to resist *infection* with hemolytic streptococci of Lancefield's Group A.

Relation of Scarlet Fever to Other Infections With Group A Hemolytic Streptococci. That scarlet fever streptococci might cause infections of the throat without a rash had long been suspected and was definitely established by Stevens and Dochez.[26] They observed that such infections occurred among persons who had negative Dick reactions, implying again that immunity against the erythrotoxin does not necessarily imply protection against the angina. Studies of the frequency of negative Dick reactions in relation to age and a history of attack have suggested that a considerable proportion of persons, perhaps 4 out of every 5, gain their antitoxic immunity (Dick-negative reaction) without having had a recognizable clinical attack of fever with rash. Such observations would indicate that infections with

hemolytic streptococci capable of causing scarlet fever, occur far more frequently without the rash than they do with it.

In this connection, a recent study by Stebbins, Ingraham and Reed[25] of the records of 1529 cases of streptococcus infection occurring in 7 milk-borne epidemics in New York State during the period 1934–36 is most interesting. The source of contamination of the milk supply in 6 out of 7 outbreaks was shown to be a cow suffering from an acute mastitis caused by a hemolytic streptococcus belonging to Group A. Three of these epidemics were classified as scarlet fever and 4 as septic sore throat. The clinical manifestations of cases observed in the various outbreaks were strikingly similar, with the exception of the presence or absence of a characteristic scarlet fever rash and desquamation. In the 3 epidemics classified as scarlet fever, a typical scarlet fever rash was observed in 60% of the cases; 40% had no rash. The character and frequency of complications were practically the same in the septic sore throat cases as in the scarlet fever cases. A previous history of scarlet fever had no influence on the frequency of infection with either clinical type of infection, but was associated with a lower incidence of rash in the scarlet fever cases. Dick tests done after recovery indicated that the proportion of persons who had become negative as a result of their illness was greater among those who had had scarlet fever than among those who had had septic sore throat.

The implications of this study may be extended to other human infections with hemolytic streptococci of Group A, such as otitis, mastoiditis, puerperal sepsis, wounds and burns (Longcope[18]). Whether or not the infection is accompanied by a *scarlet rash* will depend upon the balance between two factors: (*a*) the ability of the invading strain to produce a sufficient quantity of erythrotoxin under the conditions of growth in the tissues; and (*b*) the ability of the host to produce sufficient quantities of anti-erythrotoxin to neutralize this toxin. If the rash becomes manifest or if the case is associated with others which show a rash, it is classified as "scarlet fever." If no rash becomes apparent, it is an "infection with hemolytic streptococci." Whether the rash is of importance in prognosis or only in diagnosis is not yet clear, as the ultimate outcome of the infection depends upon the ability of the organism progressively to invade the tissues. To what extent production of erythrotoxin facilitates this invasion is unknown.

Public Health Implications. From these considerations, it appears that neither from the point of view of specificity of the etiologic organisms nor from the point of view of clinical manifestations is scarlet fever a distinct disease. Just as the hemolytic streptococci which cause it merge into the other streptococci of Lancefield Group A, so the classical disease syndrome merges into those of related infections caused by this group. Accordingly, scarlet fever should be regarded simply as a clinical manifestation of infection with one of the types of the Group A streptococci.

If this view be adopted, then it follows logically that any program of prevention should deal with this whole group of infections and not simply with those which show a rash. This applies to efforts to develop a satisfactory artificial immunity as well as efforts to control by quarantine and isolation.

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REFERENCES.

(1.) **Ando, K.**, **Kurauchi, K.**, and **Nishimura, H.**: J. Immunol., **18**, 223, 1930. (2.) **Andrewes, F. W.**, and **Christie, E. N.**: Sp. Rep. Series, No. 169, Med. Res. Council, London, 1932. (3.) **Bliss, W. P.**: Bull. Johns Hopkins Hosp., **31**, 173, 1920. (4.) **Colebrook, L.**, **Maxtell, W. R.**, and **Johns, A. M.**: J. Path. and Bact., **41**, 521, 1935. (5.) **Davis, L. J.**, and **Guzdar, J. S.**: Ibid., **43**, 197, 1936. (6.) **Dochez, A. R.**, **Avery, O. T.**, and **Lancefield, R. C.**: J. Exp. Med., **30**, 179, 1919. (7.) **Eagles, G. H.**: (*a*) Brit. J. Exp. Path., **5**, 199, 1924; (*b*) Ibid., **7**, 286, 1926. (8.) **Fraser, F. H.**: (*a*) Canad. Pub. Health J., **27**, 53, 1937; (*b*) Trans. Roy. Soc. Canada, Sec. V, **28**, 81, 1934. (9.) **Gordon, M. H.**: Brit. Med. J., **1**, 632, 1921. (10.) **Green, C. A.**: J. Hyg., **35**, 93, 1935. (11.) **Griffith, F.**: (*a*) Ibid., **25**, 385, 1926; **26**, 363, 1927; (*b*) Ibid., **34**, 542, 1934. (12.) **Hare, R.**: J. Path. and Bact., **41**, 499, 1935. (13.) **Hare, R.**, and **Maxtell, W. R.**: Ibid., p. 513. (14.) **James, S. R.**: J. Hyg., **24**, 415, 1926. (15.) **Kirkbride, M. B.**, and **Wheeler, M. W.**: J. Immunol., **13**, 19, 1927. (16.) **Lancefield, R. C.**: J. Exp. Med., **57**, 571, 1933. (17.) **Lancefield, R. C.**, and **Hare, R.**: Ibid., **61**, 335, 1935. (18.) **Longcope, W. T.**: Am. J. Med. Sci., **195**, 577, 1938. (19.) **McGibbon, J. P.**: J. Hyg., **34**, 1, 1934. (20.) **McLachlan, D. G. S.**: Ibid., **26**, 84, 1927. (21.) **McLachlan, D. G. S.**, and **Mackie, T. J.**: Ibid., **27**, 225, 1928. (22.) **Pope, A. S.**: Am. J. Hyg., **6**, 389, 1926. (23.) **Sherman, J. N.**: Bacteriol. Rev., **1**, 1, 1937. (24.) **Smith, J.**: (*a*) J. Hyg., **25**, 165, 1926; **26**, 420, 1927; (*b*) Ibid., **26**, 420, 1927. (25.) **Stebbins, E. L.**, **Ingraham, H. S.**, and **Reed, E. A.**: Am. J. Pub. Health, **27**, 1259, 1937. (26.) **Stevens, F. A.**, and **Dochez, A. R.**: J. Am. Med. Assn., **86**, 1110, 1926. (27.) **Swift, H. F.**, **Lancefield, R. C.**, and **Goodner, K.**: Am. J. Med. Sci., **190**, 445, 1935. (28.) **Toyoda, T.**, and **Fugati, Y.**: Lancet, **1**, 73, 1930. (29.) **Trask, J. D.**, and **Blake, F. G.**: J. Am. Med. Assn., **101**, 753, 1933. (30.) **Veldee, M. V.**: Pub. Health Rep., U. S. P. H. S., **52**, 819, 1937; **53**, 909, 1938. (31.) **Woods, H. M.**: Sp. Rep. Series, No. 180, Med. Res. Council, London, 1933.

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